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<p>(21) International Application Number: PCT/US94/11832 (22) International Filing Date: 20 October 1994 (20.10.94) (30) Priority Data: 08/141,168 21 October 1993 (21.10.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/141,168 (CIP) Filed on 21 October 1993 (21.10.93) (71) Applicant (for all designated States except US): G. D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HANSEN, Donald, W., Jr. [US/US]; 5250 West Brown Street, Skokie, IL 60077 (US). CURRIE, Mark, G. [US/US]; 404 Mason Ridge Drive, St. Charles, MO 63304 (US). HALLINAN, E., Ann [US/US]; 135 Barton Avenue, Evanston, IL 60202 (US). FOK, Kam, F. [US/US]; 13146 Strawberry Way, St. Louis, MO 63146 (US). HAGEN, Timothy, J. [US/US]; 875 Sugar Hill Drive,</p>		<p>Manchester, MO 63021 (US). BERGMANIS, Aija, A. [US/US]; 2149 Westview Drive, Des Plaines, IL 60018 (US). KRAMER, Steven, W. [US/US]; 8832 Kenneth Drive #1A, Des Plaines, IL 60016 (US). LEE, Len, F. [US/US]; 2496 Annapolis Way, St. Charles, MO 63303 (US). METZ, Suzanne [US/US]; 525 Westernmill Drive, Chesterfield, MO 63017 (US). MOORE, William, M. [US/US]; 1622 Boone Drive, St. Charles, MO 63303 (US). PETERSON, Karen, B. [US/US]; 340 Ashwood Court, Vernon Hills, IL 60061 (US). PITZELE, Barnett, S. [US/US]; 7924 North Tripp Avenue, Skokie, IL 60076 (US). SPANGLER, Dale, P. [US/US]; 30 Kimberly Court, Deerfield, IL 60015 (US). WEBBER, R., Keith [US/US]; 1702 Fairwood, St. Peters, MO 63376 (US). TOTH, Mihaly, V. [HU/US]; 1031 Clardge Place, St. Louis, MO 63122 (US). TRIVEDI, Mahima [IN/US]; 2600 Gold Road #410, Glenview, IL 60025 (US). TJOENG, Foe, S. [US/US]; 875 Sugar Hill Drive, Manchester, MO 63021 (US). (74) Agents: BENNETT, Dennis, A. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680- 5110 (US). (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: AMIDINO DERIVATIVES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS</p>		
<p>(57) Abstract</p>		
<p>The current invention discloses useful pharmaceutical compositions containing amidino derivatives of formula (I) as nitric oxide synthase inhibitors.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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AMIDINO DERIVATIVES USEFUL AS
NITRIC OXIDE SYNTHASE INHIBITORS

5 Background of the Invention

This application is a continuation-in-part of U.S. Patent Application Serial No. 08/141,168 filed October 21 1993.

10

Field of the Invention

The present invention relates to amidino derivatives, pharmaceutical compositions containing amidino derivatives, and to their use in therapy, in particular their use as
15 nitric oxide synthase inhibitors.

Related Art

20 It has been known since the early 1980's that the vascular relaxation brought about by acetylcholine is dependent on the presence of the endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity
25 of nitric oxide (NO) as a vasodilator has been known for well over 100 years and NO is the active component of amylnitrite, glyceryltrinitrite and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway
30 by which NO is synthesized from the amino acid L-arginine by the enzyme NO synthase.

NO is the endogenous stimulator of the soluble guanylate cyclase and is involved in a number of biological
35 actions in addition to endothelium-dependent relaxation including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al. Biochemical Pharmacology, 38: 1709-1715 (1989) and

in a number of conditions, particularly conditions which involve systemic hypotension such as toxic shock and therapy with certain cytokines.

5 The synthesis of NO from L-arginine can be inhibited by the L-arginine analogue, L-N-monomethyl-arginine (L-NMMA) and the therapeutic use of L-NMMA for the treatment of toxic shock and other types of systemic hypertension has been proposed (WO 91/04024 and GB-A-2240041). The
10 therapeutic use of certain other NO synthase inhibitors apart from L-NMMA for the same purpose has also been proposed in WO 91/04024 and in EP-A-0446699.

It has recently become apparent that there are at
15 least three types of NO synthase as follows:

- (i) a constitutive, Ca^{++} /calmodulin dependent enzyme, located in the endothelium, that releases NO in response to receptor or physical stimulation.
- (ii) a constitutive, Ca^{++} /calmodulin dependent
20 enzyme, located in the brain, that releases NO in response to receptor or physical stimulation.
- (iii) a Ca^{++} independent enzyme which is induced after activation of vascular smooth muscle, macrophages, endothelial cells, and a number of other cells by endotoxin
25 and cytokines. Once expressed this inducible NO synthase synthesizes NO for long periods.

The NO released by the constitutive enzymes acts as a transduction mechanism underlying several physiological
30 responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading microorganisms. It also appears that the adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result largely from the
35 effects of NO synthesized by the inducible NO synthase.

There is also a growing body of evidence that NO may

also known that NO synthesis is increased in rheumatoid arthritis. Accordingly, further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune and/or inflammatory conditions affecting the joints, for example arthritis.

Conditions in which there is an advantage in inhibiting NO production from L-arginine include systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy. Further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune diseases and/or inflammatory conditions such as those affecting the joints, for example arthritis or inflammatory bowel disease, cardiovascular ischemia, diabetes, hyperalgesia (allodynia) cerebral ischemia (Both focal ischemia, thrombotic stroke and global ischemia, secondary to cardiac arrest) and other CNS disorders mediated by NO.

Some of the NO synthase inhibitors proposed for therapeutic use so far, and in particular L-*NMMA*, are non-selective in that they inhibit both the constitutive and the inducible NO synthase. Use of such a non-selective NO synthase inhibitor requires that great care be taken in order to avoid the potentially serious consequences of over-inhibition of the constitutive NO-synthase including hypertension and possible thrombosis and tissue damage. In particular, in the case of the therapeutic use of L-*NMMA* for the treatment of toxic shock it has been recommended that the patient must be subject to continuous blood pressure monitoring throughout the treatment. Thus, while non-selective NO synthase inhibitors have therapeutic utility provided that appropriate precautions are taken, NO synthase inhibitors which are selective for the inducible

greater extent than the constitutive NO synthase would be of even greater therapeutic benefit and easier to use.

WO 94/12165, WO 94/14780, WO93/13055, EP 0446699A1 and U.S. Patent No. 5,132,453 disclose compounds that inhibit nitric oxide synthesis and preferentially inhibit the inducible isoform of nitric oxide synthase. The disclosures of which are hereby incorporated by reference in their entirety as if written herein.

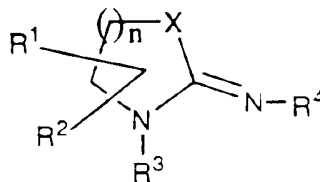
Brief Description of the Drawings

Figure 1 shows the effect of orally administered 2-iminopiperidine (mg/kg) on LPS-induced increase in plasma nitrites in rat.

Summary of the Invention

In a broad aspect, the present invention is directed to inhibiting or modulating nitric oxide synthesis in a subject in need of such inhibition or modulation by administering a compound which preferentially inhibits or modulates the inducible isoform of nitric oxide synthase over the constitutive isoforms of nitric oxide synthase.

The invention further relates to a pharmaceutical composition comprising a compound having the formula (I):



(I)

and salts, pharmaceutically acceptable esters and prodrugs thereof, wherein:

X is selected from the group consisting of:

alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;

n = 0 to about 7;

5

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon, -CONR⁵R⁶, -SO₂NR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals can be optionally substituted with one or more of the following:

hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, haloalkyl, -SO₂NR⁵R⁶ and -SO₂R⁵ wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

25

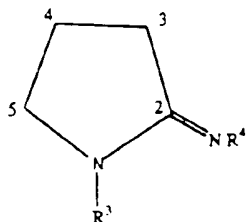
and R¹, R², may optionally together form an alicyclic hydrocarbon, heterocycly or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R³, R⁴ are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy;

35

with the proviso that when $n=1$



5

and R^1 and/or R^2 are at position 3 or 4, neither R^1 or R^2 is aryl; and

together with at least one non-toxic pharmaceutical
10 acceptable carrier.

n is preferably 1,2,3,4,5,6, or 7, more preferably n is 1-5, still more preferred n is 1-4, most preferred n is 1-3.

15

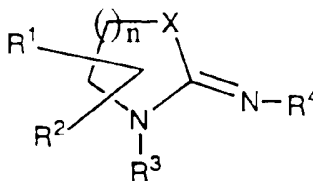
Compounds and compositions defined above have usefulness as inhibitors of nitric oxide synthase. These compounds also preferentially inhibit the inducible form over the constitutive form.

20

Detailed Description of the Invention

A preferred embodiment of the present invention is a pharmaceutical composition of the formula;

25



X is selected from the group consisting of methylene,

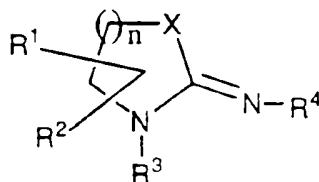
n is an integer 0 to 5;

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, haloalkyl, aromatic hydrocarbon and alicyclic hydrocarbon wherein all said radicals are optionally substituted with one or more of the following: carboxyl, carboalkoxy, amino, lower alkoxy, lower thioalkoxy and lower alkyl wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, and carboalkoxy ;

and R¹, R², may optionally together form an alicyclic hydrocarbon or aromatic hydrocarbon; and

R³, R⁴ are independently selected from the group consisting of hydrogen and hydroxy.

Another preferred embodiment of the present invention is a compound of the formula:



and salts, pharmaceutically acceptable ester and prodrugs thereof, wherein:

X is selected from the group consisting of methylene, nitrogen, oxygen, sulfur, SO, or SO₂;

n = 0 to about 7;

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower

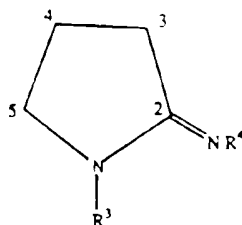
haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon, -CONR⁵R⁶, -SO₂nR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals are optionally substituted with one or more of the following: hydroxy, alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxy alkylaryloxy, haloalkyl, -SO₂NR⁵R⁶ and -SO₂R⁵ wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

and R¹, R², may optionally together form an alicyclic hydrocarbon, heterocycly or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R³, R⁴ are hydrogen, hydroxy, and alkyloxy;

R⁵ and R⁶ are independently selected from the group consisting of hydrogen, lower alkyl, and aryl;

with the proviso that when n=1



30

and R¹ and/or R² are at position 3 or 4, neither R¹ or R²

cannot be both H, or be a haloalkyl and where N=3 R¹ cannot be Methyl at position 7.

The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Salts of the compounds of formula (I) can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

While it may be possible for the compounds of formula (I) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. According to a further aspect, the present invention provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and

disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into
5 association a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the
10 active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for
15 oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water
20 liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding,
25 optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface
30 active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be
35 formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include

may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention are suitable for use in the treatment of various diseases.

per day. The dose range for adult humans is generally from 5mg to 2g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at
5 such dosage or as a multiple of the same, for instance, units containing 5mg to 500mg, usually around 10mg to 200mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form
10 will vary depending upon the host treated and the particular mode of administration.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound
15 employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

20

The compounds of formula (I) are preferably administered orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant
25 physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

30

As utilized herein, the term "lower alkyl", alone or in combination, means an acyclic alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms.
35 Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl,

The term "lower alkenyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Examples of suitable alkenyl radicals include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "lower alkynyl" refers to an unsaturated acyclic hydrocarbon radicals in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Examples of suitable alkynyl radicals include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "alicyclic hydrocarbon" means a aliphatic radical in a ring with 3 to about 10 carbon atoms, and preferably from 3 to about 6 carbon atoms. Examples of suitable alicyclic radicals include cyclopropyl, cyclopropylenyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-ylenyl, cyclohexenyl and the like.

The term "aromatic hydrocarbon radical" means 4 to about 16 carbon atoms, preferably 6 to about 12 carbon atoms, more preferably 6 to about 10 carbon atoms. Examples of suitable aromatic hydrocarbon radicals include phenyl, naphthyl, and the like.

The term "acyloxy" means 1 to about 4 carbon atoms. Suitable examples include alkanoyloxy, benzoyloxy and the like.

The term "heterocyclic radical" means a saturated or unsaturated cyclic hydrocarbon radical with 4 to about 10 carbon atoms, preferably about 5 to about 6; wherein 1 to

aromatic hydrocarbon radical. Suitable examples include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazonlinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

The term "lower alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4 carbon atoms. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "lower thioalkoxy" means the same as "alkoxy" except sulfur replaces oxygen.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "haloalkyl" means a lower alkyl as defined above having 1-5 preferably 1-3 halogens attached to said lower alkyl chain.

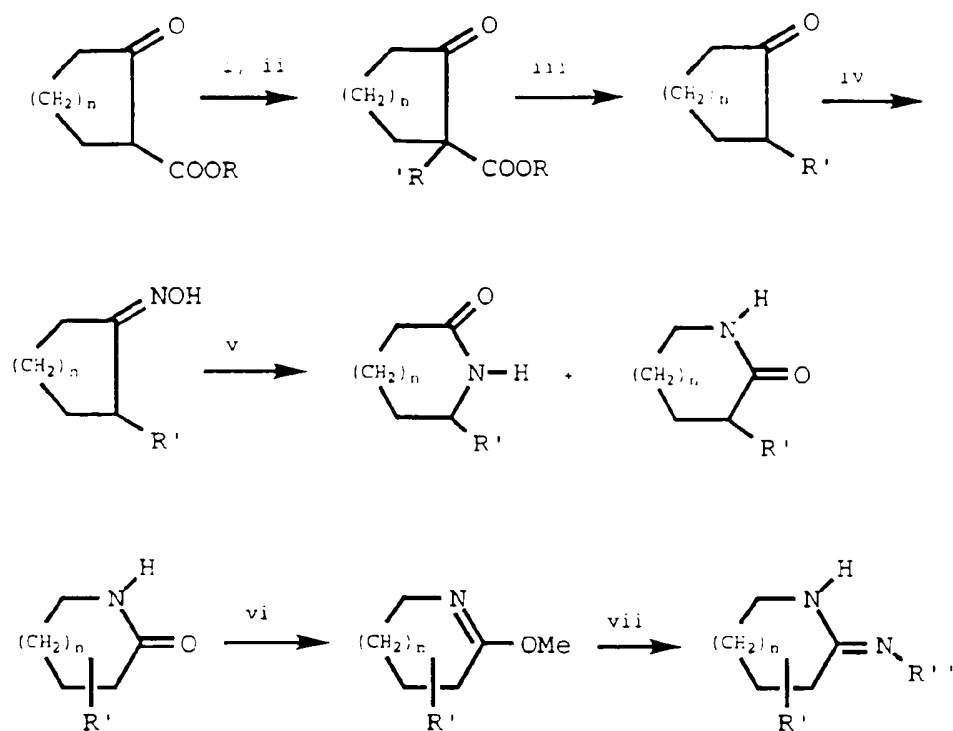
The term "prodrug" refers to a compound that is made more active in vivo.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

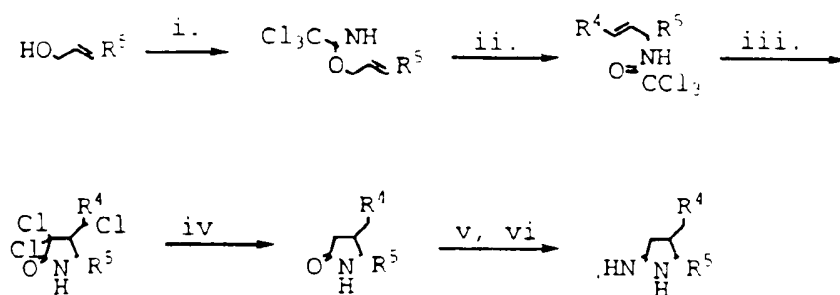
- 5 The following schemes can be used to practice the present invention.

SCHEME I

5 **Legend:**

- i. NaH/DMF;
- ii. R'Br;
- iii. LiCl/DMSO/H₂O/heat;
- iv. NH₂OH·HCl/NaOAc/EtOH/H₂O/Acetone;
- 10 vi. Me₃O⁺BF₄⁻/CH₂Cl₂;
- vii. R''NH₂/MeOH/Heat

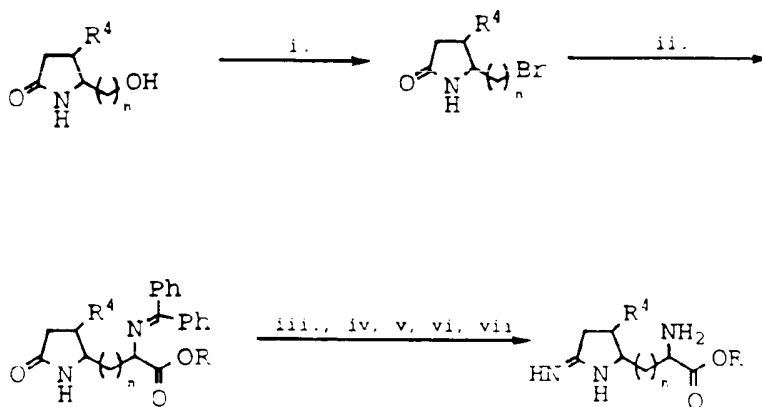
SCHEME II

**Legend:**

- i. Base,
 CCl_3CN
 ii. 140°C
 iii.
 $(\text{Ph}_3\text{P})_2\text{RuCl}_2$
 iv. Bu_3SnH
 v. $(\text{CH}_3)_3\text{OBF}_4$
 vi. NH_4Cl

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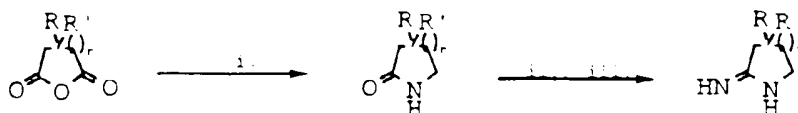
SCHEME III

**Legend:**

- i. CBr_4 , Ph_3P
 ii. Base, N-(Diphenylmethylene)glycine ester
 iii. Acid
 iv. PG addition
 v. $(\text{CH}_3)_3\text{OBF}_4$

17 bis

SCHEME IV

**Legend:**

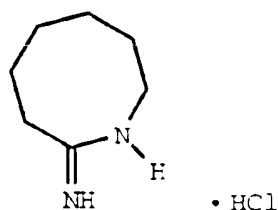
- i. H_2 , Pd on Alumina, NH_4OH
- ii. $(CH_3)_3OBF_4$
- iii. NH_4Cl

The invention is illustrated by the following
 5 examples. Some of the compounds disclosed are publicly
 available from the source cited.

EXAMPLE 1

10

2-Imino-heptamethyleneimine hydrochloride



- 15 To a 50mL flask was added 5 g (0.04 mol) of 2-oxo-heptamethyleneimine and 15 mL of benzene. This was stirred at reflux while 4.8 g (0.038mol) of dimethylsulfate were added dropwise. After the addition was complete, stirring was continued at reflux for 18
 20 hours. The heat was then removed, the reaction mixture was diluted with ethyl acetate (EtOAc) and washed with two 100 mL portions of aqueous potassium carbonate (K_2CO_3). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 4.2 g of the iminoether as a yellow

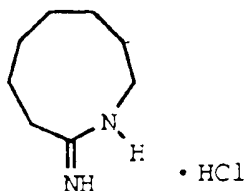
mol) of ammonium chloride was added. This mixture was stirred at 25 °C for three days. Removal of the solvent in vacuo afforded 1.7 g (48%) of the 2-imino-heptamethyleneimine hydrochloride as a white solid, mp 166-175 °C. $MH^+ = 127$.

Elemental analysis: $C_7H_{14}N_2 \cdot HCl \cdot 1/4H_2O$

	C	H	N
10 Calculated:	50.30	9.35	16.76
Found:	49.95	9.22	17.12

EXAMPLE 2

2-Imino-octamethyleneimine hydrochloride



5

To a 100 mL flask was added 5 g (0.035 mol) of 2-oxo-octamethyleneimine and 15 mL of benzene. This was stirred at reflux while 4.4 g (0.035 mol) of dimethylsulfate was added dropwise. After the addition were complete, stirring was continued at reflux for 18 hours. The heat was then removed, the reaction mixture was diluted with EtOAc and washed with two 100 mL portions of aqueous potassium carbonate. The organic layer was dried (MgSO_4), filtered and concentrated to afford 4.4 g of the iminoether as a yellow oil. The iminoether was dissolved in 50 mL of anhydrous EtOH and 1.5 g (0.028 mol) of ammonium chloride was added. This mixture was stirred at 25 °C for six days. Removal of the solvent in vacuo afforded 2.75 g (45%) of the 2-imino-octamethyleneimine hydrochloride as a white solid, mp 108-128 °C. $\text{MH}^+ = 141$.

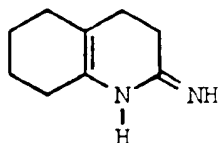
Elemental analysis: $C_8H_{16}N_2 \cdot HCl \cdot 1/3 H_2O$

25

	C	H	N
Calculated:	52.77	9.74	15.35
Found:	53.05	9.41	14.98

EXAMPLE 3

3,4,5,6,7,8-hexahydro-2[1H]-quinolineimine hydroiodide



5

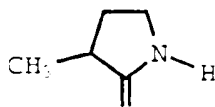
• HCl

3,4,5,6,7,8-Hexahydro-2[1H]-quinolinone (3.0 g, 20 mmol),
2,4-bis(4-methoxy-phenyl)1,3-dithia-2,4-diphosphetane 2,4-
disulfide (4.0 g, 10 mmol), and 100 ml of toluene were
10 mixed and refluxed for three hours. The dark brown
solution was cooled to room temperature, and filtered.
The filtrate was rotary evaporated. The residue was
dissolved in methylene chloride (CH_2Cl_2) and applied to a
column of silica gel equilibrated with CH_2Cl_2 . The
15 thioamide rich fractions, identified by mass spectroscopic
analyses, were combined and evaporated. The residue (0.38
g, 2.3 mmol) was treated with methyl iodide (0.36 g, 2.6
mmol) in acetone at 20 °C for four hours. After rotary
evaporation, the residue was washed with (Et_2O), several
20 times. The residue was treated with ammonia-saturated EtOH
at 20 °C for 12 hours. After evaporation, the residue was
washed with Et_2O , and recrystallized from a mixture of
EtOH and Et_2O . The product was isolated as pale yellow
solid and the mass spectrum was consistent with the
25 proposed structure. ($\text{MH}^+ = 150.1$); m.p. 150-155 °C.

EXAMPLE 4

2-Imino-3-methyltetramethyleneimine hydriodide

30

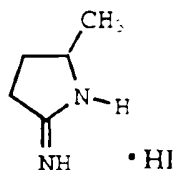


The title compound was prepared by the method of EXAMPLE 3. 3-Methyl-2-pyrrolidinone (5.0 g, 50 mmol) was converted to the thioamide which was reacted with methyl iodide, and treated subsequently with ammonia-saturated ethyl alcohol. The product was isolated as a white amorphous solid with mass spectrum consistent with the proposed structure. (MH⁺ = 98.4); m.p. 73-75 °C.

EXAMPLE 5

10

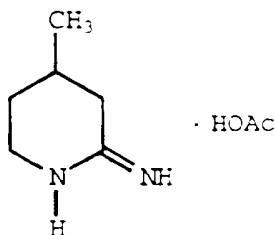
2-Imino-5-methyltetramethyleneimine hydriodide



15 The method of preparation of 3,4,5,6,7,8-nexahydro-2[1H]quinolineimine hydriodide, EXAMPLE 3, was used to convert 5-methyl-2-pyrrolidone to the title compound which was obtained as white solid. The mass spectrum of the product was found to be consistent with the proposed structure. (MH⁺ = 98.4); m.p. 83-85 °C.

EXAMPLE 6

25 2-Imino-4-methylpiperidine acetate



2-Amino-4-methylpyridine (1.56 g; 15 mmol) and 5%

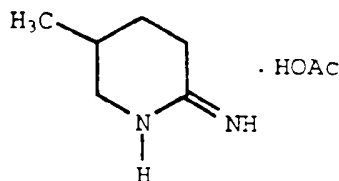
hydrogenation apparatus at 55 psi of hydrogen overnight. The catalyst was removed by filtration and the filtrate was diluted with water to 250 mL, and lyophilized to yield a light tan powder. The powder was recrystallized from warm ethanol/ether to give 0.3 g of white solid. mp 181-182°C. A second crop of white solid was obtained (0.85 g; mp 180-182°C). MH⁺ = 113; ¹H NMR (D₂O): δ 3.32 - 3.16 (m, 2H); 2.54 - 2.46 (m, 1H); 2.10 - 2.00 (m, 1H); 1.80 - 1.70 (m, 2H); 1.74 (s, 3H); 1.32 - 1.25 (m, 1H); 0.87 (d, J = 6.6 Hz, 3H).

Elemental analysis: C₆H₁₂N₂•CH₃COOH

	C	H
15 Calculated:	55.79	9.36
Found:	55.85	9.22

EXAMPLE 7

20 2-Imino-5-methylpiperidine acetate



The method of preparation of 2-imino-4-methylpiperidine acetate, EXAMPLE 6, was used to convert 2-amino-5-methylpyridine to the title compound which was obtained as a white solid. The analysis of the product was found to be consistent with the proposed structure. m.p. 175-178 °C. MH⁺ = 113; ¹H NMR (D₂O): δ 3.28 - 3.21 (m, 1H); 2.79 - 2.70 (m, 1H); 2.49 - 2.43 (m, 2H); 1.79 - 1.67 (m, 2H); 1.73 (s, 3H); 1.30 - 1.23 (m, 1H); 0.82 (d, J = 6.6 Hz, 3H).

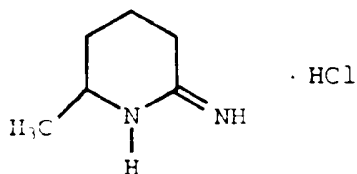
23

	C	H
Calculated:	55.79	9.36
Found:	55.81	9.39

5

EXAMPLE 8

2-Imino-6-methylpiperidine hydrochloride



10

The method of preparation of 2-imino-4-methylpiperidine acetate, EXAMPLE 6, was used to convert 2-amino-6-methylpyridine to the title compound which was obtained as a white solid. The analysis of the product was found to be consistent with the proposed structure. m.p. 160-162 °C. MH^+ = 113; 1H NMR (D_2O): δ 3.58 - 3.40 (m, 1H); 2.60 - 2.35 (m, 2H); 1.95 - 1.70 (m, 2H); 1.68 - 1.50 (m, 1H); 1.40 - 1.35 (m, 1H); 1.05 (d, J = 6.6 Hz, 3H).

20

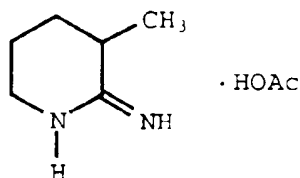
Elemental analysis: $C_6H_{12}N_2 \cdot HCl$

	C	H	N
Calculated:	48.49	8.82	18.85
25 Found:	48.32	9.01	18.70

24

EXAMPLE 9

2-imino-3-methylpiperidine acetate



5

The method of preparation of 2-imino-3-methylpiperidine acetate, EXAMPLE 6, was used to convert 2-amino-6-methylpyridine to the title compound which was obtained as a white solid. The analysis of the product was found to be consistent with the proposed structure. m.p. 88-100 °C. MH⁺ = 113 ; ¹H NMR (D₂O): δ 3.22 - 3.15 (m, 2H); 2.67 - 2.55 (m, 1H); 1.80 - 1.40 (m, 4H); 1.75 (s, 3H); 1.17 (d, J = 7.2 Hz, 3H).

15

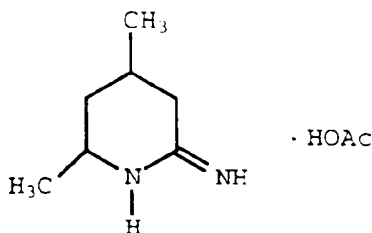
Elemental analysis: C₆H₁₂N₂·CH₃COOH·3/4H₂O

	C	H	N
Calculated:	51.73	9.50	15.08
20 Found:	51.87	9.29	15.04

EXAMPLE 10

2-imino-4,6-dimethylpiperidine acetate

25



25

as a white solid. The analysis of the product was found to be consistent with the proposed structure. m.p. 163-166 °C. $MH^+ = 127$; 1H NMR (D_2O): δ 3.48 - 3.40 (m, 1H); 2.52 - 2.40 (m, 1H); 2.07 - 1.95 (m, 1H); 1.85 - 1.75 (m, 2H); 1.75 (s, 3H); 1.12 (d, $J = 6.3$ Hz, 3H); 1.02 - 0.92 (m, 1H); 0.86 (d, $J = 6.3$ Hz, 3H).

Elemental analysis: $C_7H_{14}N_2 \cdot CH_3COOH$

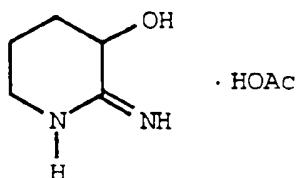
10

	C	H	N
Calculated:	58.04	9.74	15.04
Found:	57.86	10.09	15.01

15

EXAMPLE 11

2-Imino-3-hydroxypiperidine acetate



20

The method of preparation of 2-imino-3-methylpiperidine acetate, EXAMPLE 6, was used to convert 2-amino-3-hydroxypyridine to the title compound which was obtained as a white solid. The analysis of the product was found to be consistent with the proposed structure. m.p. 128-130 °C. $MH^+ = 115$; 1H NMR (D_2O): δ 4.34 - 4.28 (m, 1H); 3.20 - 3.10 (m, 2H); 2.05 - 1.50 (m, 4H); 1.71 (s, 3H).

25

Elemental analysis: $C_7H_{10}N_2O \cdot CH_3COOH$

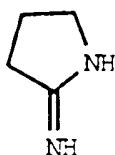
30

	C	H	N
Calculated:	48.27	6.10	16.08
Found:	48.04	6.48	16.00

Additional compounds of this invention include:

EXAMPLE 12

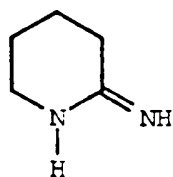
- 5 2-iminopyrrolidine hydrochloride; E. J. Moriconi and A. A. Cevasco, J. Org. Chem. 33, 2109-2111 (1968).



10

EXAMPLE 13

2-Iminopiperidine hydrochloride; Aldrich Chemical Co.

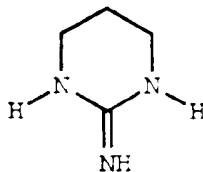


15

EXAMPLE 14

2-Iminotetrahydropyrimidine hemihydrosulfate; D. J. Brown and R. F. Evans, J. Chem. Soc. 4039-4045 (1962).

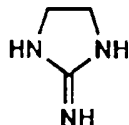
20



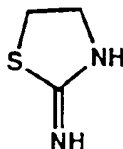
EXAMPLE 15

2-Iminoimidazolidine D. Stefanye and W. C. Howard, J.
Amer. Chem. Soc., 77, 761-762 (1955).

5

**EXAMPLE 16**

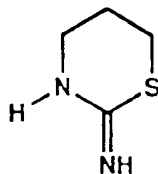
10 2-Iminothiazolidine hydrochloride; Aldrich Chemical Co.



15

EXAMPLE 17

2-Imino-3-thiapiperidine hydrochloride; D. L. Klayman and
T. S. Woods, J. Org. Chem., 39, 1819-1823 (1974).

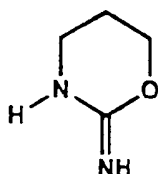


20

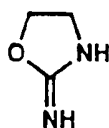
EXAMPLE 18

2-Imino-3-oxopiperidine hydrochloride; B. Adcock and A. Lawson, J. Chem.Soc. 474-479 (1965).

5

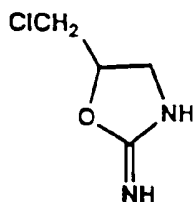
**EXAMPLE 19**

10 2-Iminooxazolidine; Transworld Chemical Inc.

**EXAMPLE 20**

15

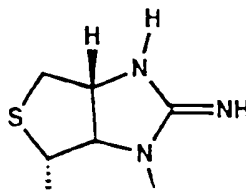
5-Chloromethyl-2-iminooxazolidine; Janssen Chimica.



20

EXAMPLE 21

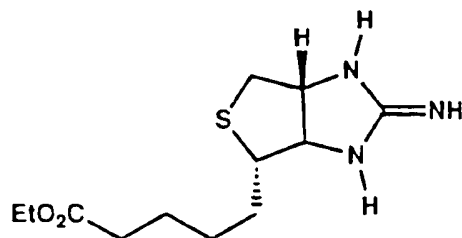
2-Iminobiotin; Sigma Chemical Co.



EXAMPLE 22

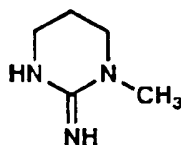
2-Iminobiotin ethyl ester.

5



EXAMPLE 23

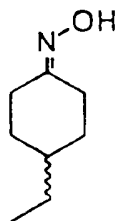
10 1-Methyl-2-iminotetrahydropyrimidine; GER 765,547



15

EXAMPLE 24

4-ethylcyclohexanone, oxime



20

A sample of 4-ethylcyclohexanone (Aldrich, 4.9 g, 38.8 mmol) was combined with $\text{NH}_2\text{OH} \cdot \text{HCl}$ (4.0 g, 58.3 mmol) and sodium acetate (NaOAc , 5.7 g, 69.8 mmol) in a mixture of ethanol (EtOH, 25 mL) and water (25 mL). The mixture was stirred at room temperature for 24 hours.

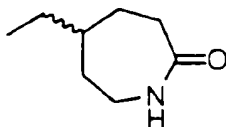
cooled to room temperature and stirred for an additional 5 days, all solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (EtOAc) and water and the organic phase was washed with 1 x 75 mL of saturated NaCl (brine), dried over Na₂SO₄, and stripped of all solvent under reduced pressure. This provided 5.5 g (100%) of the title compound as light yellow mobile oil. This material showed a retention time of 9.83 min (100% purity by peak area integration) on a Shimadzu GC-14A gas chromatograph (GC) with a 0.25 mm x 25 M methyl, 5% phenylsilicone column and NMR and IR spectra consistent with the assigned structure.

Elemental analysis: C₈H₁₅NO · H₂O (MW = 159.23)

	C	H	N
Calculated:	60.35	10.76	8.80
Found:	60.64	9.25	8.41

EXAMPLE 25

5-ethyl-hexahydro-1H-azepin-2-one



25

A 5.3 g (37.7 mmol) sample of the title material of EXAMPLE 24 was added to a dropping funnel containing 6 mL of 80% H₂SO₄. After using a stirring rod to obtain a turbid solution, this mixture was added dropwise (10 min) to 5 mL of 80% H₂SO₄ stirred magnetically and maintained at 120 °C with an external oil bath. Within 5 minutes of the start of addition an exotherm was noted and the temperature of the reaction rose to 160 °C before cooling again to 120 °C. Ten

with water (20 mL) and brought to pH 6 with concentrated
NH₄OH. This solution was further diluted with 75 mL of water
and extracted with 3 x 75 mL of CH₂Cl₂. The combined organic
phase was washed with 1 x 50 mL of brine, dried (Na₂SO₄),
5 filtered, and stripped of all solvent under reduced pressure.
The oily residue was purified by HPLC on silica gel to yield
3.73 g (70%) of the title product as a cream colored solid.
This material had a GC retention time of 13.17 min and peak
area integration of 100% under conditions identical to those
10 used for the product of EXAMPLE 24.

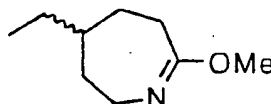
Elemental analysis: C₈H₁₅NO · 0.05 H₂O (MW = 142.12)

	C	H	N
15 Calculated:	67.61	10.71	9.86
Found:	67.47	10.67	9.90

EXAMPLE 26

20

4-ethyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

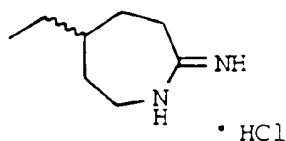


25 To a magnetically stirred slurry of trimethyloxonium
tetrafluoroborate (Lancaster, 0.62 g, 4.2 mmol) in CH₂Cl₂ (15
mL) under argon (Ar) was added the title product of EXAMPLE
25 (0.50 g, 3.5 mmol). This mixture was stirred at room
temperature for 12 h before it was diluted with 10 mL of
30 CH₂Cl₂ and partitioned between 40 mL of saturated KHCO₃ and
50 mL of EtOAc. The organic phase was separated, dried over
Na₂SO₄, filtered, and stripped of all solvent under reduced
pressure to provide the crude title product as a pale yellow

8.56 min (100%) and NMR and IR sprectra consistent with the indicated product.

EXAMPLE 27

5-ethyl-hexahydro-1H-azepin-2-imine, monohydrochloride



The title product of EXAMPLE 26 (0.28 g, 1.80 mmol) and 0.11 g (2.0 mmol) of ammonium chloride (NH₄Cl) were refluxed in 20 mL of methanol (MeOH) under a nitrogen atmosphere for 3.5 h. After cooling the reaction to room temperature, it was filtered, stripped of all solvent under reduced pressure, and partitioned between 20 mL of water and 25 mL of EtOAc. The organic and aqueous phases were separated and the aqueous phase was washed with another 25 mL portion of EtOAc before it was lyophilized to provide 0.27 g (80%) of the white solid title material.

HRMS (EI) calcd for C₈H₁₆N₂ m/e 140.131, found m/e 140.131. ¹H NMR(CD₃OD): δ 3.50-3.36 (m, 2H), 2.79-2.60 (m, 2H), 1.99-2.08 (m, 1H), 1.96-1.87 (m, 1H), 1.56 (m, 1H), 1.36 (m, 2H) 1.27-1.12 (m, 2H), 0.94 (t, 3H, J=7.5 Hz).

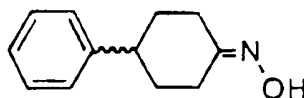
Elemental analysis: C₈H₁₆N₂ · HCl · 0.1 H₂O · 0.2 NH₄Cl
(MW = 189.19)

25

	C	H	N	Cl
Calculated:	50.79	9.59	15.26	22.49
Found:	50.71	9.48	16.30	22.45

EXAMPLE 28

4-phenylcyclohexanone, oxime



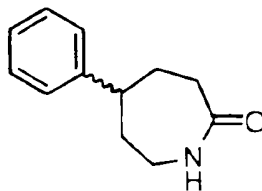
A sample of 4-phenylcyclohexanone (Aldrich, 10.0 g, 57.4 mmol) was converted to the title compound by the method of EXAMPLE 24 using 6.0 g (86.1 mmol) of hydroxylamine hydrochloride and 8.5 g (103.3 mmol) of NaOAc in a mixture of 75 mL of EtOH and 50 mL of water. The procedure produced 10.2 g (94%) of the title material as a white solid.

Elemental analysis: C₁₂H₁₅NO (MW = 189.26)

	C	H	N
Calculated:	76.16	7.99	7.40
Found:	75.96	7.89	7.33

EXAMPLE 29

hexahydro-5-phenyl-1H-azepin-2-one



To the title product of EXAMPLE 28 (9.0 g, 47.6 mmol) in 50 mL of acetone was added 1N NaOH (52.4 mL, 52.4 mmol). After cooling this mixture in an ice bath, benzene sulfonylchloride (8.5 g, 48.0 mmol) was added drop-wise over 5 minutes to the stirred reaction mixture maintained under a N₂ atmosphere.

The reaction was allowed to warm to room temperature and

mixture and washed with acetone to yield 4.2 g of the title material. The filtrate was concentrated and partitioned between EtOAc and brine. The organic layer was dried (Na₂SO₄), filtered, and stripped of all solvent under reduced pressure. The residue solid was triturated with EtOAc/n-hexane (1:1) and filtered to provide an additional 2.9 g (total yield = 80%) of the title lactam.

Elemental analysis: C₁₂H₁₅NO (MW = 189.26)

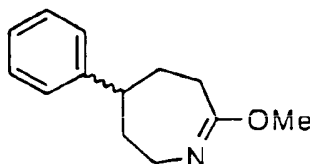
10

	C	H	N
Calculated:	76.16	7.99	7.40
Found:	75.95	8.16	7.28

15

EXAMPLE 30

3,4,5,6,-tetrahydro-7-methoxy-4-phenyl-2H-azepine



20

The product of EXAMPLE 29 (2.0 g, 10.5 mmol) was reacted with trimethyloxonium tetrafluoroborate (2.0 g, 13.6 mmol) by the method of EXAMPLE 26 to yield 1.9 g (89%) of the title material.

25

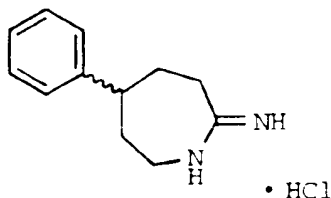
Elemental analysis: C₁₃H₁₇NO · 0.5 H₂O (MW = 209.23)

	C	H	N
Calculated:	74.63	8.51	6.69
Found:	74.77	8.14	6.65

30

EXAMPLE 31

hexahydro-5-phenyl-1H-azepin-2-imine, monohydrochloride



The product of EXAMPLE 30 (1.7 g, 8.6 mmol) in 20 mL of MeOH was reacted with ammonium chloride (0.43 g, 8.0 mmol) by the method of EXAMPLE 27 to yield 1.7 g (91%) of the title material.

HRMS (EI) calcd for $C_{12}H_{16}N_2$ m/e 188.131, found m/e 188.133. 1H NMR(CD_3OD): δ 7.33-7.26 (m, 2H), 7.25-7.17 (m, 3H), 3.60-3.53 (m, 2H), 2.98-2.87 (m, 2H), 2.78-2.69 (m, 1H), 2.17-2.08 (m, 1H), 2.05-1.98 (m, 1H), 1.80-1.69 (m, 2H).

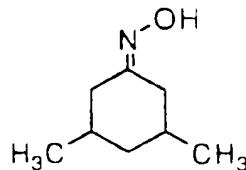
Elemental analysis: $C_{12}H_{16}N_2 \cdot HCl \cdot 0.33 H_2O$ (MW = 230.68)

	C	H	N	Cl
20 Calculated:	62.48	7.72	12.14	15.37
Found:	62.41	7.54	12.13	15.63

EXAMPLE 32

25

3,5-dimethylcyclohexanone, oxime



37

A sample of 3,5-dimethylcyclohexanone (TCI, 22.6 g, 180 mmol) was converted to the title compound by the method of EXAMPLE 24 using 18.7 g (270 mmol) of hydroxylamine hydrochloride and 26.6 g (324 mmol) of NaOAc in a mixture of 200 mL of EtOH and 110 mL of water. The procedure produced 23.1 g (94%) of the title material as a white solid.

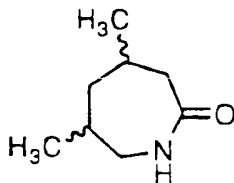
Elemental analysis: $C_8H_{15}NO \cdot 0.1 H_2O$ (MW = 143.02)

10		C	H	N
	Calculated:	67.19	10.71	9.79
	Found:	67.37	10.52	9.78

15

EXAMPLE 33

hexahydro-4,6-dimethyl-1H-azepine-2-one



20

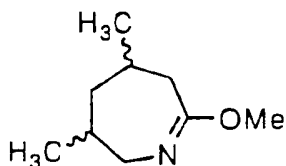
A sample of the product of EXAMPLE 32 (10.0 g, 69.9 mmol) was converted to the title compound as a mixture of two diastereomeric pairs by the method of EXAMPLE 25 using 22 mL of 80% H_2SO_4 . The procedure produced 8.4 g (85%) of the title material as a pale yellow tacky solid.

Elemental analysis: $C_8H_{15}NO$ (MW = 141.21)

30		C	H	N
	Calculated:	68.04	10.71	9.92
	Found:	67.92	10.04	9.83

EXAMPLE 34

3,4,5,6-tetrahydro-7-methoxy-3,5-dimethyl-2H-azepine



The product of EXAMPLE 33 (2.0 g, 14.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (2.7 g, 18.4 mmol) by the method of EXAMPLE 26 to yield 1.9 g (73%) of the title material.

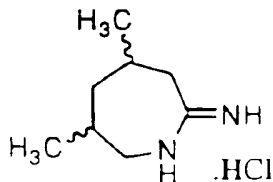
Elemental analysis: $C_9H_{17}NO \cdot 0.125 H_2O$ (MW = 157.49)

	C	H	N
15 Calculated:	68.64	11.04	8.89
Found:	68.66	11.14	8.87

EXAMPLE 35

20

hexahydro-4,6-dimethyl-1H-azepin-2-imine,
monohydrochloride



The product of EXAMPLE 34 (1.75 g, 8.6 mmol) in 25 mL of MeOH was reacted with ammonium chloride (0.48 g, 9.0 mmol) by the method of EXAMPLE 27 to yield 1.4 g (83 %) of the title material.

HRMS (EI) calcd for $C_8H_{16}N_2$ m/e 140.131, found m/e 140.130.
 1H NMR(CD_3OD): δ 3.26-3.18 (m, 1H), 2.42 (m, 1H), 1.91 (m, 1H), 1.85-1.62 (m, 2H), 1.09 (d, 3H, $J=6.8$ Hz), 0.95 (d, 3H, $J=6.8$ Hz).

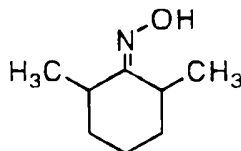
5

Elemental analysis: $C_8H_{16}N_2 \cdot HCl \cdot 0.25 H_2O$ (MW = 181.195)

	C	H	N	Cl
Calculated:	53.03	9.74	15.46	19.57
10 Found:	53.19	9.85	15.46	19.26

EXAMPLE 36

15 2,6-dimethylcyclohexanone, oxime



A sample of 2,6-dimethylcyclohexanone (Aldrich, 20.0 g, 158.5
20 mmol) was converted to the title compound by the method of
EXAMPLE 24 using 16.5 g (237.6 mmol) of hydroxylamine
hydrochloride and 23.4 g (285.1 mmol) of NaOAc in a mixture
of 150 mL of EtOH and 100 mL of water. The procedure
produced 20.3 g (88 %) of the title material as a white
25 crystalline solid.

Elemental analysis: $C_8H_{15}NO \cdot 0.25 H_2O$ (MW = 145.72)

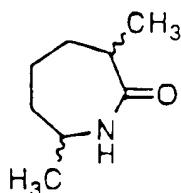
	C	H	N
30 Calculated:	65.94	10.72	9.61
Found:	65.74	10.45	9.67

EXAMPLE 37

hexahydro-3,7-dimethyl-1H-azepin-2-one

Diastereomeric pair-A and Diastereomeric pair-B

5



A sample of the product of EXAMPLE 36 (8.14 g, 57.6 mmol) was converted to the title mixture of two diastereomeric pairs by the method of EXAMPLE 25 using 15 mL of 80% H₂SO₄. Normal phase silica gel chromatography was used to separate the two diastereomeric pairs by elution with 3-10% isopropanol/n-heptane. The procedure generated 3.3 g (41 %) of the title enantiomeric pair-A eluting first from the column and 1.05 g (13%) material of the title enantiomeric pair-B eluting second from the column both as white solids.

Enantiomeric Pair-A:

Elemental analysis: C₈H₁₅NO · 0.05 H₂O (MW = 142.12)

20

	C	H	N
Calculated:	67.61	10.71	9.86
Found:	67.83	10.71	9.87

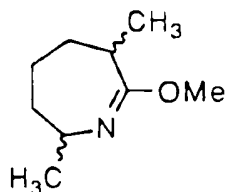
25 Enantiomeric Pair-B:

Elemental analysis: C₈H₁₅NO (MW = 141.214)

	C	H	N
Calculated:	68.04	10.71	9.92
30 Found:	68.94	10.88	9.43

EXAMPLE 38

3,4,5,6-tetrahydro-7-methoxy-2,6-dimethyl-2H-azepine
Enantiomeric pair-A

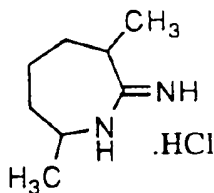


Enantiomeric pair-A of EXAMPLE 37 (2.0 g, 14.1 mmol) was
reacted with trimethyloxonium tetrafluoroborate (2.7 g, 18.4
10 mmol) by the method of EXAMPLE 26 to yield 1.9 g (86%) of the
title material as a clear volatile liquid.

EXAMPLE 39

15

hexahydro-3,7-dimethyl-1H-azepin-2-imine, monohydrochloride
Enantiomeric pair-A



20

The product of EXAMPLE 38 (1.24 g, 8.0 mmol) in 25 mL of MeOH
was reacted with ammonium chloride (0.37 g, 6.8 mmol) by the
method of EXAMPLE 27 to yield 1.23 g (91%) of the title
material.

25

MS (EI) calcd for C₈H₁₆N₂ m/e 140.131, found m/e 140 (100%).
¹H NMR(CD₃OD): δ 3.89-3.79 (m, 1H), 3.10-3.00 (m, 1H), 1.98-

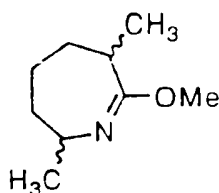
42

Elemental analysis: $C_8H_{16}N_2 \cdot HCl \cdot 0.125 H_2O \cdot 0.05 NH_4Cl$
(MW = 181.62)

	C	H	N	Cl
Calculated:	52.91	9.68	15.81	20.50
5 Found:	52.89	9.63	15.49	20.76

EXAMPLE 40

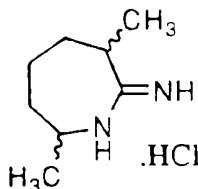
3,4,5,6-tetrahydro-7-methoxy-2,6-dimethyl-2H-azepine
10 Enantiomeric pair-B



Enantiomeric pair-B of EXAMPLE 37 (510 mg, 3.6 mmol) was
15 reacted with trimethyloxonium tetrafluoroborate (694 mg, 4.7
mmol) by the method of EXAMPLE 26 to yield 480 mg (86%) of
the title material as a clear volatile liquid.

EXAMPLE 41

20 hexahydro-3,7-dimethyl-1H-azepin-2-imine, monohydrochloride
Enantiomeric pair-B



25

The product of EXAMPLE 40 (380 mg, 2.4 mmol) in 15 mL of MeOH
and 5 mL of CH_2Cl_2 was reacted with ammonium chloride (104

43

MS (EI) calcd for $C_8H_{16}N_2$ m/e 140.131, found m/e 140.132 (100%). 1H NMR(CD_3OD): δ 3.85 (m, 1H), 3.00 (m, 1H), 1.95-1.70 (m, 5H), 1.40 (m, 1H), 1.40 (s, 2H), 0-7 Hz, 1.0 (s, 3H, J=6 Hz)

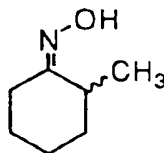
5

Elemental analysis: $C_8H_{16}N_2 \cdot HCl \cdot 0.1 H_2O \cdot 0.1 NH_4Cl$
(MW = 183.84)

	C	H	N	Cl
10 Calculated:	52.27	9.65	16.00	21.21
Found:	52.44	10.16	15.85	21.23

EXAMPLE 42

15 2-methylcyclohexanone, oxime



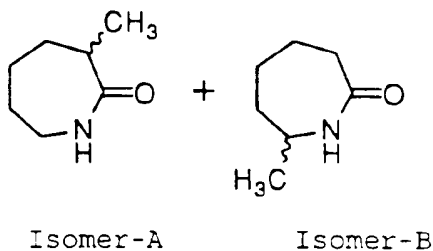
A sample of 2-methylcyclohexanone (Aldrich, 11.2 g, 100.0 mmol) was converted to the title compound by the method of EXAMPLE 24 using 13.9 g (200.0 mmol) of hydroxylamine hydrochloride and 17.2 g (210.0 mmol) of NaOAc in a mixture of 160 mL of EtOH and 160 mL of water. The procedure produced 10.1 g (79%) of the title material as a white solid.

25

EXAMPLE 43

hexahydro-3-methyl-1H-azepin-2-one, mixture with hexahydro-7-methyl-1H-azepin-2-one

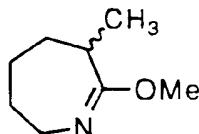
5



A sample of the product of EXAMPLE 42 (5.1 g, 40.0 mmol) was
10 converted to the title compound mixture of two regioisomers
by the method of EXAMPLE 25 using 10 mL of 80% H₂SO₄. The
procedure produced 3.1 g (62%) of the title materials. This
mixture was subjected to silica gel chromatography eluting
with 3-7% isopropanol/n-heptane to obtain Isomer-A (525 mg)
15 and Isomer-B (735 mg).

EXAMPLE 44

3,4,5,6-tetrahydro-7-methoxy-6-methyl-2H-azepine
20

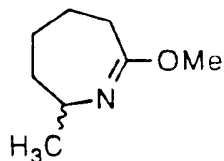


The Isomer-A product of EXAMPLE 43 (511 mg, 4.1 mmol) was
reacted with trimethyloxonium tetrafluoroborate (227 mg, 5.5
25 mmol) by the method of EXAMPLE 26 to yield, after
chromatography, 505 mg (87%) of the title material.

45

EXAMPLE 45

3,4,5,6-tetrahydro-2-methoxy-1-methyl-2H-azepine



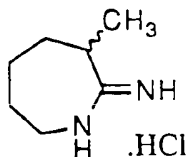
5

The Isomer-B product of EXAMPLE 43 (752 mg, 6.0 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.15 g, 7.8 mmol) by the method of EXAMPLE 26 to yield, after
10 chromatography, 780 mg (92%) of the title material.

EXAMPLE 46

hexahydro-3-methyl-1H-azepin-2-imine, monohydrochloride

15



The product of EXAMPLE 44 (294 mg, 2.1 mmol) in 14.5 mL of MeOH was reacted with ammonium chloride (103 mg, 2.0 mmol) by
20 the method of EXAMPLE 27 to yield 260 mg (77%) of the title material.

MS (EI) calcd for C₇H₁₄N₂ m/e 126.116, found m/e 126 (100%).
1H NMR(CD₃OD): δ 3.51-3.42 (m, 2H), 3.06-3.00 (m, 1H), 1.99-
25 1.93 (m, 1H), 1.82-1.73 (m, 3H), 1.61-1.50 (m, 2H), 1.30 (d, 3H, J=7.14 Hz).

Elemental analysis: C₇H₁₄N₂ · HCl · 0.2 H₂O · 0.1 NH₄Cl (MW = 171.62)

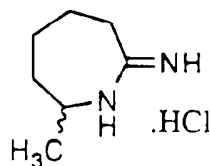
46

	C	H	N	Cl
Calculated:	48.99	9.28	17.14	22.72
Found:	48.95	9.60	17.29	22.50

5

EXAMPLE 47

hexahydro-7-methyl-1H-azepin-2-imine, monohydrochloride



10

The product of EXAMPLE 45 (125 mg, 0.89 mmol) in 9.0 mL of MeOH was reacted with ammonium chloride (44.0 mg, 0.83 mmol) by the method of EXAMPLE 27 to yield 101 mg (63%) of the title material.

15

MS (EI) calcd for $C_7H_{14}N_2$ m/e 126.116, found m/e 126 (100%). 1H NMR(CD_3OD): δ 3.77 (m, 1H), 2.77 (ddd, 1H), 2.62 (m, 1H), 2.03-1.95 (m, 2H), 1.84 (m, 1H), 1.7 (m, 3H), 1.51-1.35 (m, 2H), 1.32 (d, 3H, $J=6.84$ Hz).

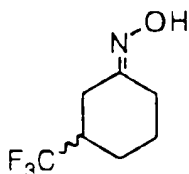
20

Elemental analysis: $C_7H_{14}N_2 \cdot HCl \cdot 0.33 H_2O \cdot 0.21 NH_4Cl$ (MW = 179.84)

	C	H	N	Cl
25 Calculated:	46.75	9.25	17.21	23.85
Found:	46.53	9.45	17.29	24.25

EXAMPLE 48

3-(trifluoromethyl)cyclohexanone, oxime



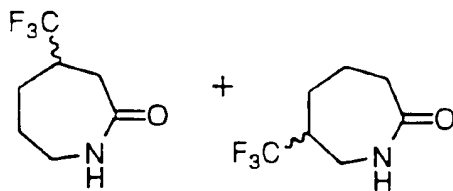
5

A sample of 3-trifluoromethylcyclohexanone (Aldrich, 3.3 g, 20.0 mmol) was converted to the title compound by the method of EXAMPLE 24 using 2.8 g (40.0 mmol) of hydroxylamine hydrochloride and 3.4 g (42.0 mmol) of NaOAc in a mixture of 30 mL of EtOH and 30 mL of water. The procedure provided 2.9 g (80%) of the title material as a white solid.

EXAMPLE 49

15

hexahydro-4-(trifluoromethyl)-1H-azepin-2-one, mixture with hexahydro-6-(trifluoromethyl)-1H-azepin-2-one



20

Isomer-A

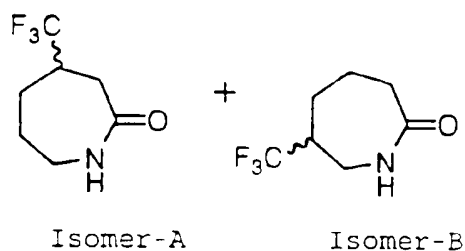
Isomer-B

A sample of the product of EXAMPLE 48 (2.3 g, 12.5 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 4 mL of 80% H₂SO₄. The procedure produced 795 mg (36%) of the title materials. This mixture of 80% Isomer-A was subjected to reverse phase HPLC eluting with acetonitrile/water to obtain only Isomer-A (330 mg).

EXAMPLE 50

hexahydro-4-(trifluoromethyl)-1H-azepin-2-one, mixture with
hexahydro-6-(trifluoromethyl)-1H-azepin-2-one

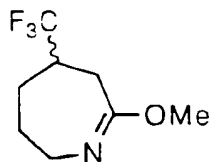
5



A sample of 3-trifluoromethylcyclohexanone (Aldrich, 1.7 g,
10 10.0 mmol) was added dropwise to a stirred mixture of 12 mL
of conc H₂SO₄ and 4 mL of CH₂Cl₂. To this mixture,
maintained at 0 -10 °C, was added 0.8 g (0.12 mmol) of sodium
azide portionwise over 1 hr. After the reaction had warmed
to room temperature and stirred overnight, it was poured into
15 50 mL of ice water and the mixture was extracted with CHCl₃
(50mL). The organic layer was washed with water, dried
(Na₂SO₄), filtered, and concentrated to the crude title
mixture that was 63% Isomer-B. This material was subjected
to reverse phase HPLC eluting with acetonitrile/water to
20 obtain only Isomer-B (438 mg).

EXAMPLE 51

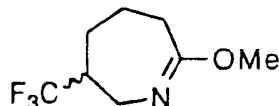
3,4,5,6-tetrahydro-7-methoxy-5-(trifluoromethyl)-2H-azepine
25



The Isomer-A product of EXAMPLE 49 (457 mg, 2.5 mmol) was
reacted with trimethyloxonium tetrafluoroborate (461 mg, 2.5 mmol)

EXAMPLE 52

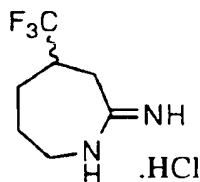
3,4,5,6-tetrahydro-7-methoxy-3-(trifluoromethyl)-2H-azepine
5



The Isomer-B product of EXAMPLE 50 (350 mg, 1.9 mmol) was
reacted with trimethyloxonium tetrafluoroborate (371 mg, 2.5
10 mmol) by the method of EXAMPLE 26 to yield, after
chromatography, 280 mg (76%) of the title material.

EXAMPLE 53

15 hexahydro-4-(trifluoromethyl)-1H-azepin-2-imine,
monohydrochloride



20 The product of EXAMPLE 51 (240 mg, 1.2 mmol) in 7.0 mL of
MeOH was reacted with ammonium chloride (66.0 mg, 1.2 mmol)
by the method of EXAMPLE 27 to yield 265 mg (94 %) of the
title material.

25 HRMS (EI) calcd for C₇H₁₁N₂F₃ m/e 180.087, found m/e 180.087.
¹H NMR(CD₃OD): δ 1.63 (m, 1H), 1.79 (m, 1H), 1.99 (m, 1H),
2.22 (m, 1H), 2.63 (m, 1H), 2.86 (dt, 1H), 2.98 (dd, 1H),
3.42-3.46 (m, 2H).

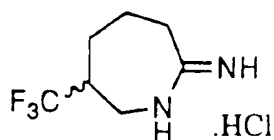
50

	C	H	N	Cl
Calculated:	36.62	5.73	13.42	18.53
Found:	36.93	5.51	13.12	18.41

5

EXAMPLE 54

hexahydro-6-(trifluoromethyl)-1H-azepin-2-imine,
monohydrochloride



10

The product of EXAMPLE 52 (77 mg, 0.39 mmol) in 3.0 mL of MeOH was reacted with ammonium chloride (21.0 mg, 0.39 mmol) by the method of EXAMPLE 27 to yield 83 mg (94%) of the title material.

HRMS (EI) calcd for C₇H₁₁N₂F₃ m/e 180.087, found m/e 180.087. ¹H NMR(CD₃OD): δ 3.7 (m, 1H), 3.57-3.66 (m, 1H), 2.85 (ddd, 1H), 2.75 (ddd, 1H), 2.53 (m, 1H), 2.2 (m, 1H), 2.1 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H).

20

Elemental analysis: C₇H₁₁N₂F₃ · HCl · 0.2 H₂O + 0.1 NH₄Cl (MW = 225.59)

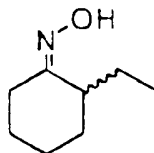
25

	C	H	N	Cl
Calculated:	37.27	5.72	13.04	17.29
Found:	37.21	5.47	12.72	16.93

51

EXAMPLE 55

2-ethylcyclohexanone oxime



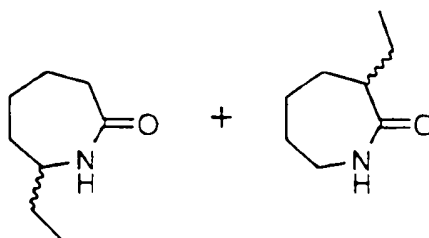
5

A sample of 2-ethylcyclohexanone (Pfaltz & Bauer, 9.5 g, 75.0 mmol) was converted to the title compound by the method of EXAMPLE 24 using 10.4 g (150 mmol) of hydroxylamine hydrochloride and 12.6 g (153.7 mmol) of NaOAc in a mixture of 120 mL each of EtOH and water. The procedure produced 9.8 g (93%) of the title material as a white solid.

EXAMPLE 56

15

7-ethyl-hexahydro-1H-azepin-2-one, mixture with 3-ethyl-hexahydro-1H-azepin-2-one



Isomer-A

Isomer-B

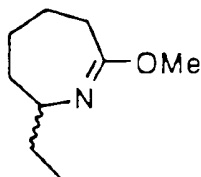
20

A sample of the product of EXAMPLE 55 (4.9 g, 34.3 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 11 mL of 80% H₂SO₄. The procedure produced 7.2 g (73%) of the title materials as a pale yellow liquid. This mixture was separated into its components by chromatography to yield 2.1 g of isomer-A and 1.1 g of isomer-B.

25

EXAMPLE 57

2-ethyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



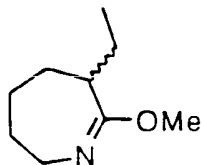
5

The Isomer-A product of EXAMPLE 56 (938 mg, 6.65 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.28 g, 8.6 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 802 mg (78%) of the title material.

EXAMPLE 58

6-ethyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

15



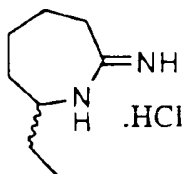
The Isomer-B product of EXAMPLE 56 (700 mg, 5.0 mmol) was reacted with trimethyloxonium tetrafluoroborate (955 mg, 6.4 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 613 mg (89%) of the title material.

20

53

EXAMPLE 59

7-ethyl-hexan-2-yl-1H-azepin-2-imine, monohydrochloride



5

The product of EXAMPLE 57 (802 mg, 5.2 mmol) in 15 mL of MeOH was reacted with ammonium chloride (225 mg, 4.2 mmol) by the method of EXAMPLE 27 to yield 627 mg (82%) of the title material.

HRMS (EI) calcd for $C_8H_{16}N_2$ m/e 140.131, found m/e 140.131.
 1H NMR(CD_3OD): δ 3.57-3.51 (m, 1H), 2.82-2.75 (m, 1H), 2.65-2.60 (m, 1H), 2.03-1.97 (m, 2H), 1.89-1.83 (m, 1H), 1.72-1.62 (m, 3H), 1.54-1.47 (m, 1H), 1.41-1.32 (m, 1H), 1.05-1.01 (t, 3H, $J = 7.45$ Hz)).

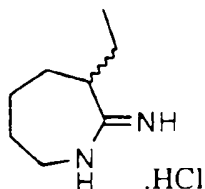
Elemental analysis: $C_8H_{16}N_2 \cdot HCl \cdot 0.1 H_2O + 0.01 NH_4Cl$
(MW = 179.03)

20

	C	H	N	Cl
Calculated:	53.67	9.71	15.85	20.06
Found:	53.62	10.13	15.86	20.02

EXAMPLE 60

3-ethyl hexahydro-2H-azepin-2-one, monohydrochloride



5

The product of EXAMPLE 58 (600 mg, 3.9 mmol) in 20 mL of MeOH was reacted with ammonium chloride (165 mg, 3.1 mmol) by the method of EXAMPLE 27 to yield 512 mg (93%) of the title material.

HRMS (EI) calcd for $C_8H_{16}N_2$ m/e 140.131, found m/e 140.132.
 1H NMR(CD₃OD): δ 3.48-3.30 (m, 2H), 2.76-2.74 (m, 1H), 1.90-1.71 (m, 4H), 1.70-1.64 (m, 4H), 1.05-1.02 (m, 3H).

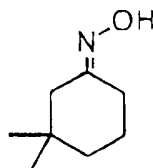
15

Elemental analysis: $C_8H_{16}N_2 \cdot HCl \cdot 0.2 H_2O + 0.01 NH_4Cl$
 (MW = 180.83)

	C	H	N	Cl
20 Calculated:	53.14	9.72	15.57	19.80
Found:	52.98	10.46	15.60	20.04

EXAMPLE 61

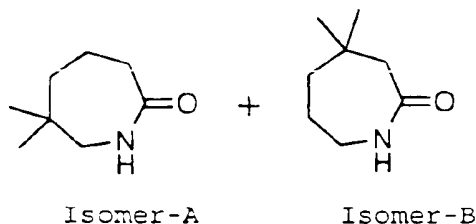
25 3,3-dimethylcyclohexanone, oxime



EXAMPLE 24 using 20.7 g (300.0 mmol) of hydroxylamine hydrochloride and 25.2 g (307.5 mmol) of NaOAc in a mixture of 400 mL of EtOH and 400 mL of water. The procedure produced 16.2 g (77%) of the title material as a pale yellow oil.

EXAMPLE 62

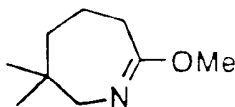
hexahydro-6,6-dimethyl-1H-azepin-2-one, mixture with
10 hexahydro-4,4-dimethyl-1H-azepin-2-one



15 A sample of the product of EXAMPLE 61 (7.1 g, 50.0 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 12.5 mL of 80% H₂SO₄. The procedure produced 6.2 g (87%) of the title materials as a light brown solid. This mixture was separated into its
20 components by chromatography to yield 1.4 g of isomer-A and 1.8 g of isomer-B.

EXAMPLE 63

25 3,4,5,6-tetrahydro-7-methoxy-3,3-dimethyl-2H-azepine

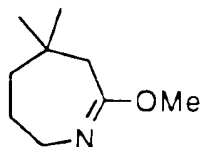


The Isomer-A product of EXAMPLE 62 (985 mg, 7.0 mmol) was
30 reacted with trimethyloxonium tetrafluoroborate (1.3 g, 9.1

EXAMPLE 64

3,4,5,6-tetrahydro-7-methoxy-5,5-dimethyl-2H-azepine

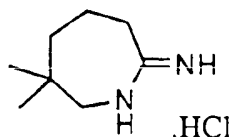
5



The Isomer-B product of EXAMPLE 62 (437 mg, 3.1 mmol) was reacted with trimethyloxonium tetrafluoroborate (573 mg, 3.9 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 265 mg (55%) of the title material.

EXAMPLE 65

15 hexahydro-6,6-dimethyl-1H-azepin-2-imine, monohydrochloride



The product of EXAMPLE 63 (490 mg, 3.2 mmol) in 18 mL of MeOH was reacted with ammonium chloride (125 mg, 2.4 mmol) by the method of EXAMPLE 27 to yield 387 mg (69%) of the title material.

MS (EI) calcd for $C_8H_{16}N_2$ m/e 140.131, found m/e 140 (100%).
25 1H NMR(CD_3OD): δ 5.80-5.72 (m, 2H), 5.62-5.58 (m, 2H), 3.2 (s, 2H), 2.68-2.63 (m, 2H), 0.95 (s, 6H).

Elemental analysis: $C_8H_{16}N_2 \cdot HCl$ (MW = 176.69)

30

C

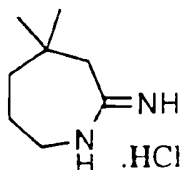
H

N

Cl

EXAMPLE 66

hexahydro-4,4-dimethyl-1H-azepin-2-imine,
5 monohydrochloride



The product of EXAMPLE 64 (260 mg, 1.7 mmol) in 10 mL of EtOH
10 was reacted with ammonium chloride (88 mg, 1.7 mmol) by the
method of EXAMPLE 27 to yield 185 mg (55%) of the title
material.

HRMS (EI) calcd for C₈H₁₆N₂ m/e 140.131, found m/e 140.132.
15 ¹H NMR(CD₃OD): δ 3.42-3.39 (m, 2H), 2.62 (s, 2H), 1.75-1.65
(m, 4H), 1.07 (s, 6H).

Elemental analysis: C₈H₁₆N₂ · HCl · 0.2 H₂O · 0.32 NH₄Cl
(MW = 197.26)

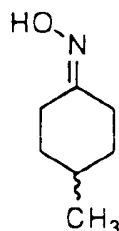
20

	C	H	N	Cl
Calculated:	48.71	9.47	16.47	23.72
Found:	48.68	9.41	16.49	24.04

58

EXAMPLE 67

4-methylcyclohexanone oxime



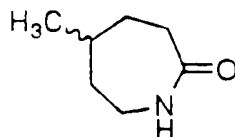
5

A sample of 4-methylcyclohexanone (Aldrich, 5.0 g, 44.6 mmol) was converted to the title compound by the method of EXAMPLE 24 using 4.6 g (66.9 mmol) of hydroxylamine hydrochloride and 6.2 g (75.8 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 4.8 g (84%) of the title material as a pale yellow oil.

EXAMPLE 68

15

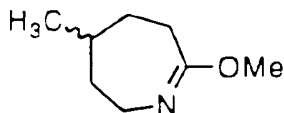
hexahydro-5-methyl-1H-azepin-2-one



20 A sample of the product of EXAMPLE 67 (4.0 g, 31.4 mmol) was converted to the title compound by the method of EXAMPLE 25 using 10 mL of 80% H₂SO₄. The procedure produced 3.2 g (80%) of the title material as a yellow oil.

EXAMPLE 69

3,4,5,6-tetrahydro-7-methoxy-4-methyl-2H-azepine



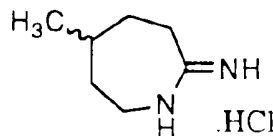
5

The product of EXAMPLE 68 (2.5 g, 19.7 mmol) dissolved in 25 mL of benzene was dried by refluxing the mixture through a Dean-Stark trap for 30 minutes. To this mixture was added dimethylsulfate (1.4 mL, 19.7 mmol) and the heating was continued for an additional 17 hours. After cooling to room temperature, the reaction was diluted with EtOAc (50 mL) and washed with 50 mL of saturated NaHCO₃. The aqueous layer was extracted with 2x100 mL EtOAc and the combined organic phase was dried (Na₂SO₄), filtered, and stripped of all solvent under reduced pressure to yield a mixture of two immiscible oils. The top lighter phase (1.6 g, 58%) was separated and identified as the title material.

20

EXAMPLE 70

hexahydro-5-methyl-1H-azepin-2-imine, monohydrochloride



25

The product of EXAMPLE 69 (750 mg, 5.3 mmol) in 3 mL of EtOH was reacted with ammonium chloride (285 mg, 5.3 mmol) by the method of EXAMPLE 27 to yield 700 mg (77%) of the title material.

30

HRMS m/z M⁺, C₇H₁₅N₂ requires 127.124; ¹H NMR (400 MHz,

60

(m, 1H), 1.9-2.0 (m, 1H), 1.75-1.89 (m, 2H), 1.14-1.28 (m, 2H), 1 (d, 3H, J = 4.2 Hz).

Elemental analysis: C₇H₁₄N₂ · 0.85 HCl · 0.8 H₂O (MW = 171.59)

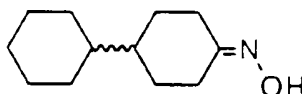
5

	C	H	N	Cl
Calculated:	48.99	9.66	16.32	17.56
Found:	49.20	8.94	16.01	17.24

10

EXAMPLE 71

4-cyclohexylcyclohexanone, oxime



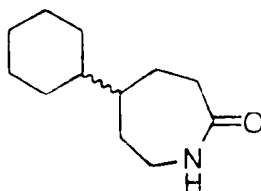
15

A sample of 4-cyclohexylcyclohexanone (Bader, 5.0 g, 27.7 mmol) was converted to the title compound by the method of EXAMPLE 24 using 2.9 g (41.6 mmol) of hydroxylamine hydrochloride and 3.9 g (47.1 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 5.3 g (97%) of the title material as a pale yellow oil.

20

EXAMPLE 72

25 5-cyclohexyl-hexahydro-1H-azepin-2-one

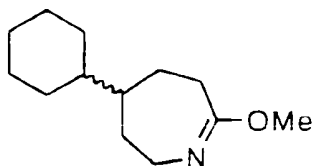


A sample of the product of EXAMPLE 71 (4.5 g, 23.0 mmol) was converted to the title compound by the method of EXAMPLE 25

30

EXAMPLE 73

4-cyclohexyl-3,4,5,6-tetrahydro-2H-azepine



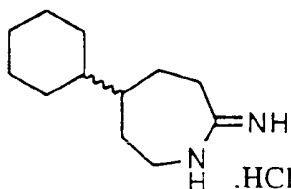
5

The product of EXAMPLE 72 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 74

5-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride



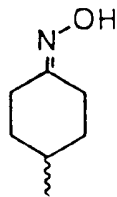
15

The product of EXAMPLE 73 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

20

EXAMPLE 75

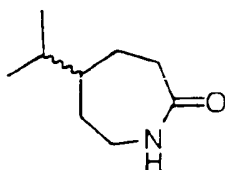
4-(1-methylethyl)cyclohexanone, oxime



A sample of 4-isopropylcyclohexanone (P & B, 3.8 g, 26.9 mmol) was converted to the title compound by the method of EXAMPLE 24 using 2.8 g (40.4 mmol) of hydroxylamine hydrochloride and 3.7 g (45.7 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 4.1 g (100%) of the title material as a clear oil.

EXAMPLE 76

10 hexahydro-5-(1-methylethyl)-1H-azepin-2-one

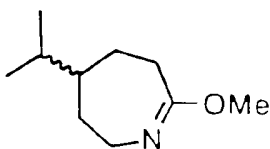


15 A sample of the product of EXAMPLE 75 (3.7 g, 24.2 mmol) was converted to the title compound by the method of EXAMPLE 25 using 10 mL of 80% H₂SO₄. The procedure produced 2.4 g (63%) of the title material after chromatography.

EXAMPLE 77

20

3,4,5,6-tetrahydro-7-methoxy-4-(1-methylethyl)-2H-azepine

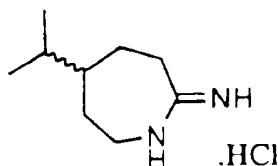


25 The product of EXAMPLE 76 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

EXAMPLE 78

hexahydro-5-(1-methylethyl)-1H-azepin-2-imine
monohydrochloride

5

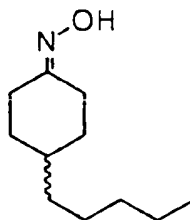


The product of EXAMPLE 77 in MeOH is reacted with ammonium
chloride by the method of EXAMPLE 27 to generate the title
10 material.

EXAMPLE 79

4-pentylcyclohexanone, oxime

15



A sample of 4-n-pentylcyclohexanone (TCI, 5.2 g, 31.0 mmol)
was converted to the title compound by the method of EXAMPLE
20 24 using 3.2 g (46.7 mmol) of hydroxylamine hydrochloride and
4.3 g (52.8 mmol) of NaOAc in a mixture of 25 mL of EtOH and
25 mL of water. The procedure produced 6.1 g (96%) of the
title material as a pale yellow liquid.

EXAMPLE 80

hexahydro-5-pentyl-1H-azepin-2-one



5

A sample of the product of EXAMPLE 79 (5.7 g, 31.4 mmol) was converted to the title compound by the method of EXAMPLE 25 using 20 mL of 80% H₂SO₄. The procedure produced 3.7 g (64%) of the title material after chromatography.

EXAMPLE 81

3,4,5,6-tetrahydro-7-methoxy-4-pentyl-2H-azepine

15



The product of EXAMPLE 80 (1.5 g, 8.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.4 g, 9.8 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 1.1 g (65%) of the title material.

EXAMPLE 82

25 hexahydro-5-pentyl-1H-azepin-2-imine, monohydrochloride



the method of EXAMPLE 27 to yield 643 mg (73%) of the title material.

HRMS (EI) calcd for $C_{11}H_{22}N_2$ m/e 182.178, found m/e 182.179.

5 1H NMR (400 MHz, D_2O) δ 3.35-3.53 (m, 2H), 2.6-2.75 (m, 2H), 1.96-2.04 (m, 1H), 1.85-1.95 (m, 1H), 1.6-1.75 (m, 1H), 1.2-1.4 (m, 10H), 0.88 (t, 3H, $J = 4$ Hz).

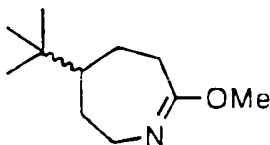
Elemental analysis: $C_{11}H_{22}N_2 \cdot 1.0 HCl \cdot 0.2 H_2O \cdot 0.15 NH_4Cl$
10 (MW = 230.40)

	C	H	N	Cl
Calculated:	57.31	10.56	13.06	17.68
Found:	57.55	10.53	13.23	17.69

15

EXAMPLE 83

4-(1,1-dimethylethyl)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



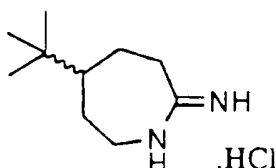
20

A sample of 4-tertbutylcaprolactam (Bader, 2.5 g, 14.8 mmol) was reacted with dimethylsulfate (1.4 mL, 14.8 mmol) by the method of EXAMPLE 69 to yield, after chromatography, 2.7 g of
25 the title material.

EXAMPLE 84

5-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-imine
monohydrochloride

5



The product of EXAMPLE 83 (2.5 g, 13.6 mmol) in 50 mL of EtOH was reacted with ammonium chloride (730 mg, 13.6 mmol) by the method of EXAMPLE 27 to yield 2.2 g (78%) of the title material.

¹H NMR (400 MHz, CD₃OD) δ 3.5 (ddd, 1H, J = 1.87, 6.08, 15.0 Hz), 3.33-3.41 (m, 1H), 2.66-2.71 (m, 2H), 2.13-2.21 (m, 1H), 2.0-2.08 (m, 1H), 1.39 (tt, 1H, J = 2.9, 11.9 Hz), 1.15-1.26 (m, 2H), 0.9 (s, 9H).

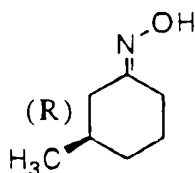
Elemental analysis: C₁₀H₂₀N₂ · 0.8 HCl · 1.125 H₂O · 0.6 NH₄Cl (MW = 249.80)

20

	C	H	N	Cl
Calculated:	47.65	10.28	14.45	19.69
Found:	47.75	9.76	14.22	19.97

EXAMPLE 85

3R-methylcyclohexanone, oxime

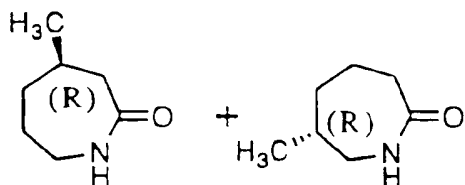


A sample of R(+)-3-methylcyclohexanone (Aldrich, 5.0 g, 44.6 mmol) was converted to the title compound by the method of EXAMPLE 24 using 4.6 g (66.9 mmol) of hydroxylamine hydrochloride and 6.2 g (75.8 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 5.7 g (100 %) of the title material as a clear oil.

EXAMPLE 86

15

hexahydro-4R-methyl-1H-azepin-2-one, mixture with hexahydro-6R-methyl-1H-azepin-2-one



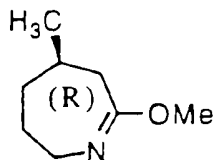
Isomer-A

Isomer-B

A sample of the product of EXAMPLE 85 (5.0 g, 39.3 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 10 mL of 80% H₂SO₄. The procedure produced 4.3 g of the title materials as a pale yellow oil. This mixture was separated into its components by chromatography to yield 215 mg of isomer-A and 318 mg of isomer-B.

EXAMPLE 87

3,4,5,6-tetrahydro-7-methoxy-5R-methyl-2H-azepine

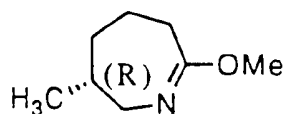


The Isomer-A product of EXAMPLE 86 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to generate the title material.

10

EXAMPLE 88

3,4,5,6-tetrahydro-7-methoxy-3R-methyl-2H-azepine



15

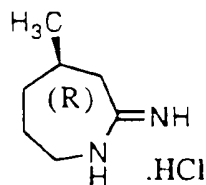
The Isomer-B product of EXAMPLE 86 (225 mg, 1.8 mmol) was reacted with trimethyloxonium tetrafluoroborate (340 mg, 2.3 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 900 mg of the crude title material.

20

EXAMPLE 89

hexahydro-4R-methyl-1H-azepin-2-imine, monohydrochloride

25

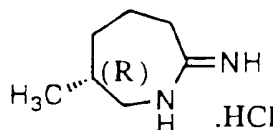


The product of EXAMPLE 87 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

5

EXAMPLE 90

hexahydro-6R-methyl-1H-azepin-2-imine, monohydrochloride



10

The product of EXAMPLE 88 (250 mg, 1.8 mmol) in 10 mL of MeOH was reacted with ammonium chloride (80 mg, 1.5 mmol) by the method of EXAMPLE 27 to yield 155 mg (44%) of the title material.

15

¹H NMR (300 MHz, D₂O) δ 3.22-3.36 (m, 2H), 2.58-2.72 (m, 2H), 1.89-1.94 (m, 2H), 1.75-1.79 (m, 1H), 1.59-1.66 (m, 1H), 1.44-1.50 (m, 1H), 0.92 (d, 3H, J = 4.2 Hz).

20

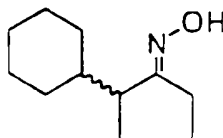
Elemental analysis: C₇H₁₄N₂ · 1.0 HCl · 0.25 H₂O · 0.55 NH₄Cl (MW = 196.60)

	C	H	N	Cl
Calculated:	42.77	9.08	18.17	27.95
25 Found:	43.07	9.04	18.42	28.37

EXAMPLE 91

2-cyclohexylcyclohexanone, oxime

30

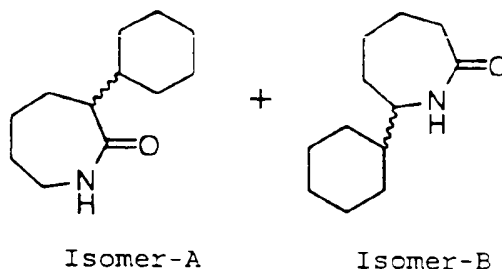


70

A sample of 2-cyclohexylcyclohexanone (Fluka, 10.0 g, 55.5 mmol) was converted to the title compound by the method of EXAMPLE 24 using 5.8 g (69.5 mmol) of hydroxylamine hydrochloride and 7.7 g (82.0 mmol) of NaOAc in a mixture of 50 mL of EtOH and 50 mL of water. The procedure produced 11.7 g of the crude title compound as pale yellow oil.

EXAMPLE 92

3-cyclohexyl-hexahydro-1H-azepin-2-one, mixture with 7-cyclohexyl-hexahydro-1H-azepin-2-one



15

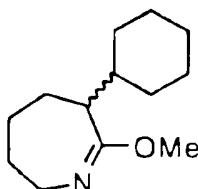
The product of EXAMPLE 91 (10.0 g, 51.2 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 29 using 9.13 g (51.7 mmol) of benzene sulfonylchloride. The crude product mixture was triturated with Et₂O to give 4.9 g of title product Isomer B. The filtrate was concentrated to provide a mixture of isomers but predominately title product Isomer A. This mixture is separated into its Isomer-A and Isomer-B components by chromatography.

25

71

EXAMPLE 93

6-cyclohexyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



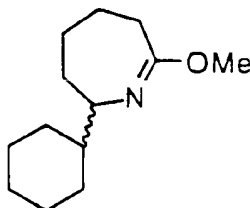
5

The Isomer-A product of EXAMPLE 92 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 94

2-cyclohexyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



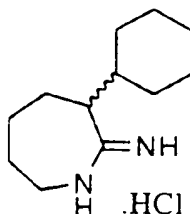
15

The Isomer-B product of EXAMPLE 92 (1.50 g, 3.6 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.48 g, 10.0 mmol) by the method of EXAMPLE 26 to yield 0.76 g (48%) of the title material as a clear liquid.

20

EXAMPLE 95

3-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride

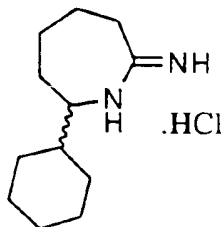


The product of EXAMPLE 93 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

10

EXAMPLE 96

7-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride



15

The product of EXAMPLE 94 (730 mg, 3.45 mmol) in 30 mL of MeOH was reacted with ammonium chloride (177 mg, 3.31 mmol) by the method of EXAMPLE 27 to yield 579 mg (75%) of the title material.

20

¹H NMR (400 MHz, D₂O) δ 3.48-3.41 (dd, J= 9.3 Hz, 1H), 2.8-2.7 (m, 1H), 2.61-2.54 (m, 1H), 2.0-1.0 (m, 17 H).

25 Elemental analysis: C₁₂H₂₂N₂ · 1.0 HCl · 0.6 H₂O (MW = 241.59)

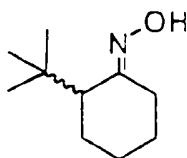
73

Calculated:	59.66	10.10	11.60	14.67
Found:	59.41	9.92	11.31	14.83

EXAMPLE 97

5

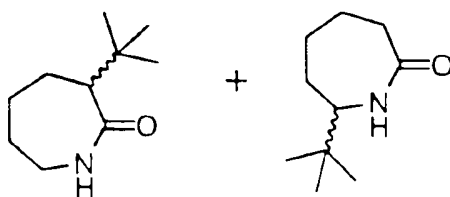
2-(1,1-dimethylethyl)cyclohexanone, oxime



- 10 A sample of 2-tert-butylcyclohexanone (Aldrich, 5.0 g, 32.4 mmol) was converted to the title compound by the method of EXAMPLE 24 using 3.4 g (48.6 mmol) of hydroxylamine hydrochloride and 4.5 g (55.0 mmol) of NaOAc in a mixture of 50 mL of EtOH and 50 mL of water. The procedure produced
- 15 5.0 g (92%) of the crude title compound.

EXAMPLE 98

- 3-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-one, mixture
- 20 with 7-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-one



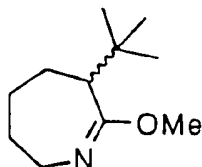
Isomer-A

Isomer-B

- 25 A sample of the product of EXAMPLE 97 (4.7 g, 27.8 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 9 mL of 80% H₂SO₄. The procedure produced 3.9 g of the title materials as a yellow solid. This mixture was separated into its components by

EXAMPLE 99

6-(1,1-dimethylethyl)-3,4,5,6-tetrahydro-7-methoxy-2H-
5 azepine

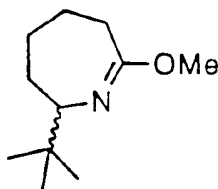


The Isomer-A product of EXAMPLE 98 (664 mg, 3.9 mmol) was
10 reacted with trimethyloxonium tetrafluoroborate (696 mg, 4.7
mmol) by the method of EXAMPLE 26 to yield, after
chromatography, 654 mg (91%) of the title material.

EXAMPLE 100

15

2-(1,1-dimethylethyl)-3,4,5,6-tetrahydro-7-methoxy-2H-
azepine



20

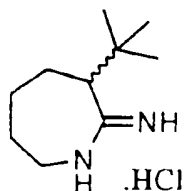
The Isomer-B product of EXAMPLE 98 (352 mg, 2.1 mmol) was
reacted with trimethyloxonium tetrafluoroborate (370 mg, 2.5
mmol) by the method of EXAMPLE 26 to yield, after
chromatography, the title material.

25

EXAMPLE 101

3-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-imine
monohydrochloride

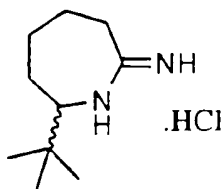
5



The product of EXAMPLE 99 (551 mg, 2.7 mmol) in 10 mL of
MeOH was reacted with ammonium chloride (145 mg, 2.7 mmol)
10 by the method of EXAMPLE 27 to yield 350 mg of the crude
title material.

EXAMPLE 102

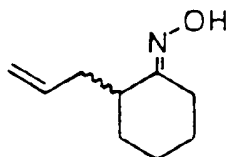
15 7-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-imine,
monohydrochloride



20 The product of EXAMPLE 100 (174 mg, 1.0 mmol) in 10 mL of
EtOH was reacted with ammonium chloride (51 mg, 1.0 mmol) by
the method of EXAMPLE 27 to yield the crude title material.

EXAMPLE 103

2-(2-propenyl)cyclohexanone, oxime



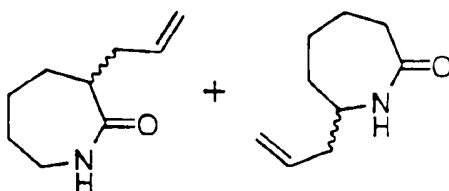
5

A sample of 2-allylcyclohexanone (Frinton, 2.0 g, 14.5 mmol) was converted to the title compound by the method of EXAMPLE 24 using 1.5 g (21.7 mmol) of hydroxylamine hydrochloride and 2.0 g (24.6 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 2.6 g of the crude title compound.

EXAMPLE 104

15

hexahydro-3-(2-propenyl)-1H-azepin-2-one, mixture with hexahydro-7-(2-propenyl)-1H-azepin-2-one



20

Isomer-A

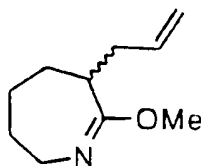
Isomer-B

The title product of EXAMPLE 103 (2.0 g, 13.0 mmol) in 15 mL of acetone containing 1N NaOH (14.3 mL, 52.4 mmol) was reacted with benzene sulfonylchloride (2.3 g, 13.1 mmol) by the method described in EXAMPLE 29. The crude reaction mixture was separated into its Isomer-A and Isomer-B components by silica gel chromatography.

77

EXAMPLE 105

3,4,5,6-tetrahydro-7-methoxy-6-(2-propenyl)-2H-azepine

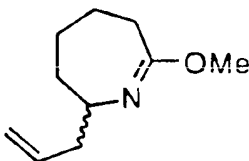


5

The Isomer-A product of EXAMPLE 104 (130 mg, 0.85 mmol) was reacted with trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 91 mg (64%) of the title material.

EXAMPLE 106

3,4,5,6-tetrahydro-7-methoxy-2-(2-propenyl)-2H-azepine



15

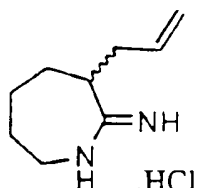
The Isomer-B product of EXAMPLE 104 (250 mg, 1.63 mmol) was reacted with trimethyloxonium tetrafluoroborate (312 mg, 2.11 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 194 mg (71%) of the title material.

20

EXAMPLE 107

hexahydro-3-(2-propenyl)-1H-azepin-2-imine
monohydrochloride

5



The product of EXAMPLE 105 (90 mg, 0.54 mmol) in 10 mL of MeOH was reacted with ammonium chloride (24.5 mg, 0.46 mmol) by the method of EXAMPLE 27 to yield 68 mg (67%) of the title material.

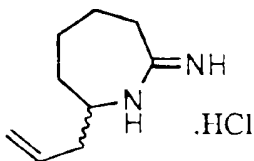
¹H NMR (300 MHz, CD₃OD) δ 5.9-5.7 (m, 1H), 5.3-5.1 (m, 2H), 3.6-3.4 (m, 2H), 3.0-2.9 (m, 1H), 2.7-2.5 (m, 1H), 2.45-2.3 (m, 1H), 2.0-1.6 (M, 6H).

15

EXAMPLE 108

hexahydro-7-(2-propenyl)-1H-azepin-2-imine,
monohydrochloride

20



The product of EXAMPLE 106 (70 mg, 0.42 mmol) in 3 mL of MeOH was reacted with ammonium chloride (21.4 mg, 0.4 mmol) by the method of EXAMPLE 27 to yield 60 mg (76%) of the title material.

25

¹H NMR (400 MHz, D₂O) δ 5.9-5.8 (m, 1H), 5.26-5.19 (m

79

1H), 2.42-2.39 (m, 2H), 2.04-1.94 (m, 2H), 1.91-1.84 (m, 1H), 1.7-1.6 (m, 1H), 1.56-1.35 (m, 2H).

Elemental analysis: $C_9H_{16}N_2 \cdot 1.0 HCl \cdot 0.75 H_2O \cdot 0.05 NH_4Cl$

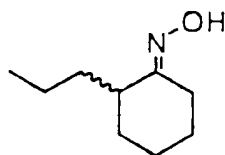
5 (MW = 204.88)

	C	H	N	Cl
Calculated:	52.76	9.20	14.01	18.17
Found:	53.13	9.06	14.05	18.32

10

EXAMPLE 109

2-propylcyclohexanone, oxime



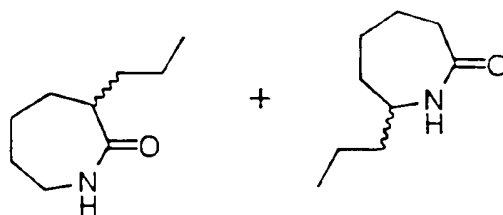
15

A sample of 2-n-propylcyclohexanone (Farchan, 19.7 g, 140.5 mmol) was converted to the title compound by the method of EXAMPLE 24 using 14.6 g (211.0 mmol) of hydroxylamine hydrochloride and 20.8 g (252.9 mmol) of NaOAc in a mixture of 150 mL of EtOH and 100 mL of water. The procedure produced 23.4 g of the crude title compound.

25

EXAMPLE 110

hexahydro-3-propyl-1H-azepin-2-one, mixture with hexahydro-7-propyl-1H-azepin-2-one

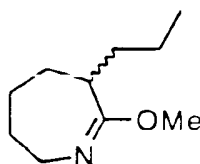


30

The product of EXAMPLE 109 (11.5 g, 74.1 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 29 using 13.2 g (74.5 mmol) of benzene sulfonylchloride. The crude pale yellow solid product mixture (6.1 g) was separated into its Isomer-A and Isomer-B components by chromatography.

EXAMPLE 111

3,4,5,6-tetrahydro-7-methoxy-6-propyl-2H-azepine



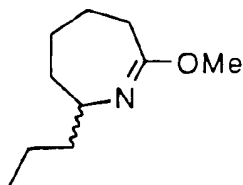
The Isomer-A product of EXAMPLE 110 (0.50 g, 3.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (0.62 g, 4.2 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 0.45 g (83%) of the title material.

Elemental analysis: $C_{10}H_{19}NO \cdot 0.1 H_2O$ (MW = 169.27)

	C	H	N
Calculated:	70.21	11.31	8.19
Found:	70.35	11.32	7.97

EXAMPLE 112

3,4,5,6-tetrahydro-7-methoxy-2-propyl-2H-azepine



5

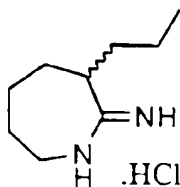
The Isomer-B product of EXAMPLE 110 (0.65 g, 4.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (0.81 g, 5.4 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 0.60 g (84%) of the title material.

Elemental analysis: $C_{10}H_{19}NO \cdot 0.125 H_2O$ (MW = 171.52)

	C	H	N
15 Calculated:	70.03	11.31	8.47
Found:	69.94	11.41	7.92

EXAMPLE 113

20 hexahydro-3-propyl-1H-azepin-2-imine, monohydrochloride



The product of EXAMPLE 111 (415 mg, 2.45 mmol) in 20 mL of MeOH was reacted with ammonium chloride (111 mg, 2.1 mmol) by the method of EXAMPLE 27 to yield 360 mg (76%) of the title material.

82

^1H NMR (400 MHz, CD_3OD) δ 3.48 (m, 2H), 2.90-2.81 (m, 1H), 1.96-1.85 (m, 1H), 1.85-1.55 (m, 7H), 1.55-1.32 (m, 2H), 1.00 (t, 3H, $J = 7.2$ Hz).

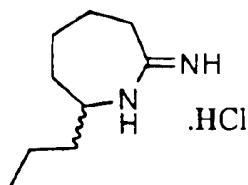
5 Elemental analysis: $\text{C}_9\text{H}_{18}\text{N}_2 \cdot 1.0 \text{ HCl} \cdot 0.15 \text{ H}_2\text{O} \cdot 0.02 \text{ NH}_4\text{Cl}$
(MW = 194.43)

	C	H	N	Cl
Calculated:	55.60	10.02	14.55	18.60
10 Found:	55.57	9.92	14.35	18.62

EXAMPLE 114

hexahydro-7-propyl-1H-azepin-2-imine, monohydrochloride

15



The product of EXAMPLE 112 (560 mg, 3.3 mmol) in 20 mL of MeOH was reacted with ammonium chloride (150 mg, 2.8 mmol) by the method of EXAMPLE 27 to yield 514 mg (78%) of the title material.

^1H NMR (400 MHz, CD_3OD) δ 3.68-3.58 (m, 1H), 2.79 (ddd, 1H, $J=14.3, 12.2, 1.9$ Hz), 2.61 (dd, 1H, $J=14.6, 6.6$ Hz), 2.06-1.95 (m, 2H), 1.90-1.81 (m, 1H), 1.75-1.32 (m, 7H), 0.98 (t, 3H, $J = 7.2$ Hz).

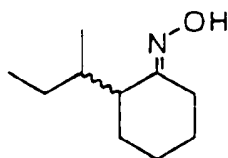
Elemental analysis: $\text{C}_9\text{H}_{18}\text{N}_2 \cdot 1.0 \text{ HCl} \cdot 0.4 \text{ H}_2\text{O} \cdot 0.05 \text{ NH}_4\text{Cl}$
(MW = 200.60)

30

	C	H	N	Cl
Calculated:	53.89	10.05	14.31	18.56

EXAMPLE 115

2-(1-methylpropyl)cyclohexanone, oxime



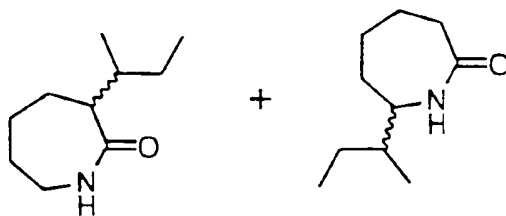
5

A sample of 2-sec-butylcyclohexanone (Lancaster, 9.9 g, 64.2 mmol) was converted to the title compound by the method of EXAMPLE 24 using 6.7 g (96.3 mmol) of hydroxylamine hydrochloride and 9.5 g (115.6 mmol) of NaOAc in a mixture of 75 mL of EtOH and 50 mL of water. The procedure produced 11.3 g of the crude title compound.

EXAMPLE 116

15

hexahydro-3-(1-methylpropyl)-1H-azepin-2-one, mixture with hexahydro-7-(1-methylpropyl)-1H-azepin-2-one



Isomer-A

Isomer-B

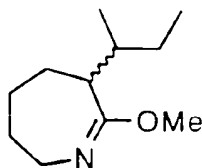
20

The product of EXAMPLE 115 is converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 80% H₂SO₄. This product mixture is separated into its Isomer-A and Isomer-B components by chromatography.

25

EXAMPLE 117

3,4,5,6-tetrahydro-7-methoxy-6-(1-methylpropyl)-2H-azepine



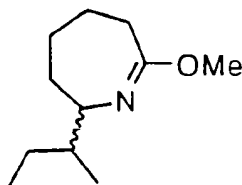
5

The Isomer-A product of EXAMPLE 116 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 118

3,4,5,6-tetrahydro-7-methoxy-2-(1-methylpropyl)-2H-azepine



15

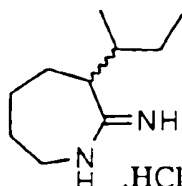
The Isomer-B product of EXAMPLE 116 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

20

EXAMPLE 119

hexahydro-3-(1-methylpropyl)-1H-azepin-2-imine,
monohydrochloride

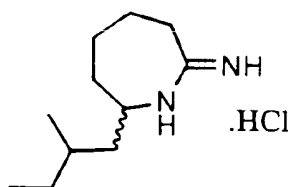
5



The product of EXAMPLE 117 in MeOH is reacted with ammonium
chloride by the method of EXAMPLE 27 to generate the title
10 material.

EXAMPLE 120

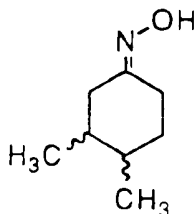
hexahydro-7-(1-methylpropyl)-1H-azepin-2-imine,
15 monohydrochloride



The product of EXAMPLE 118 in MeOH is reacted with ammonium
20 chloride by the method of EXAMPLE 27 to generate the title
material.

EXAMPLE 121

3,4-dimethylcyclohexanone, oxime



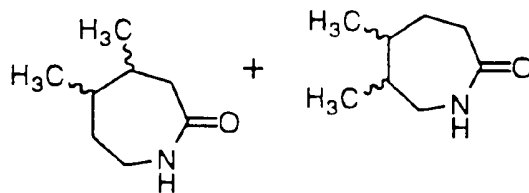
5

A sample of 3,4-dimethylcyclohexanone (TCI, 9.0 g, 71.0 mmol) was converted to the title compound by the method of EXAMPLE 24 using 7.4 g (107.0 mmol) of hydroxylamine hydrochloride and 9.9 g (121.0 mmol) of NaOAc in a mixture of 50 mL of EtOH and 50 mL of water. The procedure yielded 2.6 g of the crude title compound.

EXAMPLE 122

15

hexahydro-4,5-dimethyl-1H-azepin-2-one, mixture with hexahydro-5,6-dimethyl-1H-azepin-2-one



20

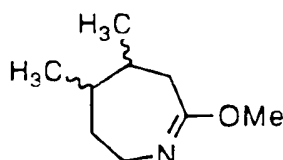
Isomer-A

Isomer-B

A sample of the product of EXAMPLE 121 (8.0 g, 56.6 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 20 mL of 80% H₂SO₄. The procedure gave 7.1 g of the title materials as an amber liquid. This mixture was separated into its component regioisomers by chromatography to yield 233 mg of

EXAMPLE 123

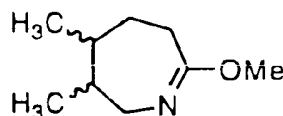
3,4,5,6-tetrahydro-7-methoxy-4,5-dimethyl-2H-azepine
5



The Isomer-A product of EXAMPLE 122 (205 mg, 1.5 mmol) was
reacted with trimethyloxonium tetrafluoroborate (279 mg, 1.9
10 mmol) by the method of EXAMPLE 26 to yield, after
chromatography, 100 mg (53%) of the title material.

EXAMPLE 124

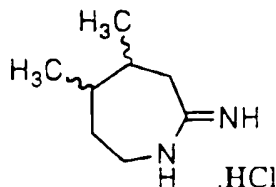
15 3,4,5,6-tetrahydro-7-methoxy-3,4-dimethyl-2H-azepine



The Isomer-B product of EXAMPLE 122 is reacted with
20 trimethyloxonium tetrafluoroborate by the method of EXAMPLE
26 to produce the title material.

EXAMPLE 125

25 hexahydro-4,5-dimethyl-1H-azepin-2-imine, monohydrochloride



The product of EXAMPLE 123 (100 mg, 0.64 mmol) in 5 mL of MeOH was reacted with ammonium chloride (29.3 mg, 547 mmol) by the method of EXAMPLE 27 to yield 68 mg (66%) of the white solid title material.

5

^1H NMR (300 MHz, D_2O) δ 3.25-3.45 (m, 2H), 2.85 (d, 1H, J = 12 Hz), 2.6 (dd, 1H, J = 9, 15 Hz), 2.05-2.08 (m, 1H), 1.9-2.0 (m, 1H), 1.4-1.61 (m, 2H), 0.94 (d, 3H, J = 9 Hz), 0.88 (d, 3H, J = 6 Hz).

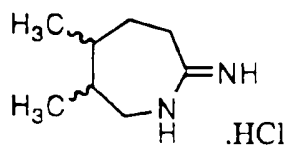
10

Elemental analysis: $\text{C}_8\text{H}_{16}\text{N}_2 \cdot 1.0 \text{ HCl} \cdot 0.01 \text{ H}_2\text{O} \cdot 0.2 \text{ NH}_4\text{Cl}$
(MW = 187.57)

	C	H	N	Cl
15 Calculated:	51.23	9.58	16.43	22.68
Found:	50.85	9.51	16.22	22.59

EXAMPLE 126

20 hexahydro-5,6-dimethyl-1H-azepin-2-imine, monohydrochloride

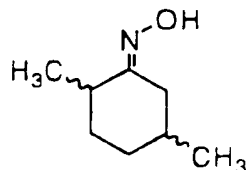


The product of EXAMPLE 124 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

25

EXAMPLE 127

2,5-dimethylcyclohexanone, oxime



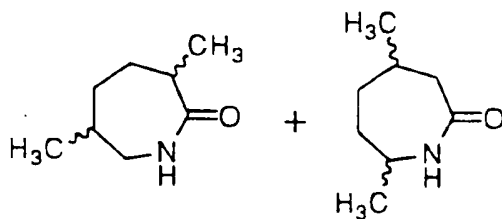
5

A sample of 2,5-dimethylcyclohexanone (TCI, 9.0 g, 71.0 mmol) was converted to the title compound by the method of EXAMPLE 24 using 7.4 g (107.0 mmol) of hydroxylamine hydrochloride and 9.9 g (121.0 mmol) of NaOAc in a mixture of 50 mL of EtOH and 50 mL of water. The procedure generated 7.1 g (71%) of the crude title compound.

EXAMPLE 128

15

hexahydro-3,6-dimethyl-1H-azepin-2-one, mixture with hexahydro-4,7-dimethyl-1H-azepin-2-one



Isomer-A

Isomer-B

20

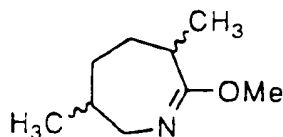
A sample of the product of EXAMPLE 127 (6.8 g, 48.5 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 20 mL of 80% H₂SO₄. The procedure produced the crude title materials. This mixture was separated into its component regioisomers by chromatography to yield no clean amount of Isomer-A title

25

90

EXAMPLE 129

3,4,5,6-tetrahydro-7-methoxy-3,6-dimethyl-2H-azepine



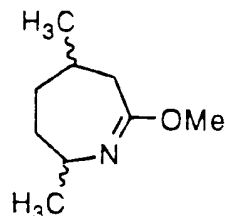
5

The Isomer-A product of EXAMPLE 128 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 130

3,4,5,6-tetrahydro-7-methoxy-2,5-dimethyl-2H-azepine



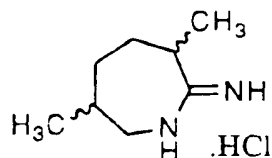
15

The Isomer-B product of EXAMPLE 128 (1.0 g, 7.1 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.3 g, 8.5 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 700 mg of the title material.

20

EXAMPLE 131

hexahydro-3,6-dimethyl-1H-azepin-2-imine, monohydrochloride

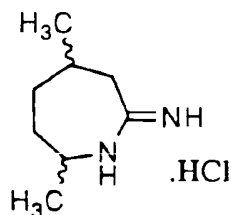


The product of EXAMPLE 129 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

10

EXAMPLE 132

hexahydro-4,7-dimethyl-1H-azepin-2-imine, monohydrochloride



15

The product of EXAMPLE 130 (250 mg, 1.6 mmol) in 2.5 mL of EtOH was reacted with ammonium chloride (86.0 mg, 1.6 mmol) by the method of EXAMPLE 27 to yield 220 mg (75%) of the white solid title material.

20

¹H NMR (400 MHz, D₂O) δ 3.7-3.8 (m, 1H), 2.7 (dd, 1H, J = 10, 12 Hz), 2.4 (d, 1H, J = 15 Hz), 1.9-2.0 (m, 1H), 1.7-1.85 (m, 2H), 1.4-1.55 (m, 2H), 1.3 (d, 6H, J = 8 Hz), 1.06 (d, 3H, J = 8 Hz).

25

Elemental analysis: C₈H₁₆N₂ · 1.06 HCl · 0.25 H₂O
(MW = 183.38)

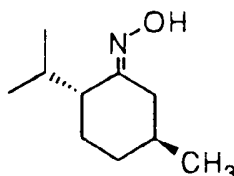
92

Calculated:	52.40	9.65	15.28	20.49
Found:	52.10	9.82	15.94	20.77

EXAMPLE 133

5

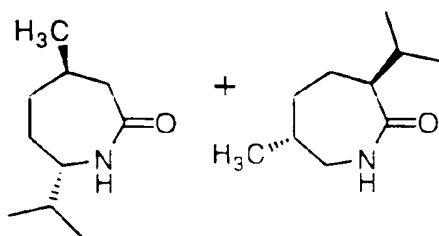
(2R-trans)-2-(1-methylethyl)-5-methylcyclohexanone, oxime



10 A sample of (-)-menthone (Aldrich, 10.0 g, 64.8 mmol) was converted to the title compound by the method of EXAMPLE 24 using 6.8 g (97.3 mmol) of hydroxylamine hydrochloride and 9.0 g (110.2 mmol) of NaOAc in a mixture of 50 mL of EtOH and 50 mL of water. The procedure produced the crude title
15 compound.

EXAMPLE 134

(4R-trans)-hexahydro-7-(1-methylethyl)-4-methyl-1H-azepin-2-one, mixture with (3S-trans)-hexahydro-3-(1-methylethyl)-6-methyl-1H-azepin-2-one
20



Isomer-A

Isomer-B

25

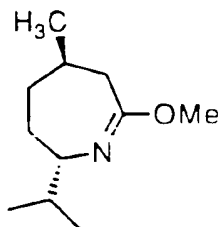
A sample of the product of EXAMPLE 133 (10.0 g, 59.0 mmol) was converted to the title compound mixture of two

This mixture was separated into its component regioisomers by chromatography to yield 3.1 g of Isomer-A title compound and 1.5 g of pure Isomer-B title compound.

5

EXAMPLE 135

(5R-trans)-3,4,5,6-tetrahydro-7-methoxy-2-(1-methylethyl)-5-methyl-2H-azepine

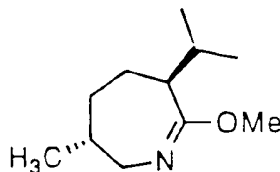


10

The Isomer-A product of EXAMPLE 134 (1.0 g, 5.9 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.1 g, 7.1 mmol) by the method of EXAMPLE 26 to yield, after
15 chromatography, 740 mg (68%) of the title material.

EXAMPLE 136

(6R-trans)-3,4,5,6-tetrahydro-7-methoxy-6-(1-methylethyl)-3-methyl-2H-azepine
20

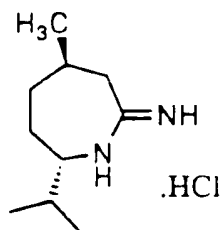


The Isomer-B product of EXAMPLE 134 (840 mg, 5.0 mmol) was
25 reacted with trimethyloxonium tetrafluoroborate (880 mg, 6.0 mmol) by the method of EXAMPLE 26 to yield, after
chromatography, 441 mg (49%) of the title material.

EXAMPLE 137

(7S-trans)-hexahydro-7-(1-methylethyl)-4-methyl-1H-azepin-2-imine, monohydrochloride

5



The product of EXAMPLE 135 (690 mg, 3.8 mmol) in 20 mL of MeOH was reacted with ammonium chloride (201 mg, 3.8 mmol) by the method of EXAMPLE 27 to yield 570 mg (73%) of the white solid title material.

HRMS (EI) calcd for $C_{10}H_{20}N_2$ m/e 168.163, found m/e 168.163. 1H NMR (400 MHz, D_2O) δ 3.4-3.5 (m, 1H), 2.7 (dd, 1H, J = 12, 15 Hz), 2.4 (bd, 1H, J = 14 Hz), 1.8-2 (m, 3H), 1.7-1.8 (m, 1H), 1.31-1.45 (m, 2H), 1.05 (d, 3H, J = 7.6 Hz), 0.95 (d, 6H, J = 8 Hz).

Elemental analysis: $C_{10}H_{20}N_2 \cdot 1.0 HCl \cdot 0.33 H_2O \cdot 0.05 NH_4Cl$ (MW = 213.36)

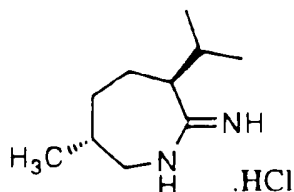
	C	H	N	Cl
Calculated:	56.23	10.33	13.40	17.40
Found:	56.28	10.81	13.57	17.58

25

EXAMPLE 138

(3S-trans)-hexahydro-3-(1-methylethyl)-6-methyl-1H-azepin-2-imine, monohydrochloride

5



The product of EXAMPLE 136 (300 mg, 1.6 mmol) in 10 mL of MeOH was reacted with ammonium chloride (70 mg, 1.3 mmol) by the method of EXAMPLE 27 to yield 240 mg (86%) of the white solid title material.

$[\alpha]_D = +33.6^\circ$ (0.53, CH₃OH)
¹H NMR (400 MHz, D₂O) δ 3.6 (bd, 1H, J = 14 Hz), 3.2 (dd, 1H, J = 4, 16 Hz) 2.35-2.45 (m, 1H), 2.2-2.3 (m, 1H), 1.95 (m, 3H), 1.65-1.75 (m, 1H), 1.42-1.52 (m, 1H), 1.0 (dd, 6H, J = 7 Hz), 0.95 (d, 3H, J = 6 Hz).

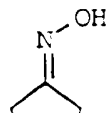
Elemental analysis: C₁₀H₂₀N₂ · 1.0 HCl · 0.33 H₂O · 0.05 NH₄Cl (MW = 213.73)

	C	H	N	Cl
Calculated:	56.20	10.45	13.11	15.76
Found:	56.58	10.24	12.70	15.88

25

EXAMPLE 139

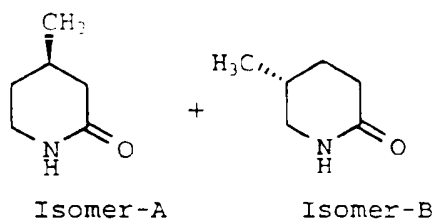
3R-methylcyclopentanone, oxime



A sample of R(+)-3-methylcyclopentanone (Aldrich, 5.0 g, 50.9 mmol) was converted to the title compound by the method of EXAMPLE 24 using 5.3 g (76.4 mmol) of hydroxylamine hydrochloride and 7.1 g (86.5 mmol) of NaOAc in a mixture of 25 mL of EtOH and 25 mL of water. The procedure produced 4.9 g (86%) of the title material as white solid.

EXAMPLE 140

4R-methylpiperidin-2-one, mixture with 5R-methylpiperidin-2-one

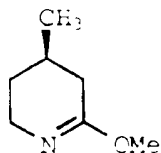


15

A sample of the product of EXAMPLE 139 (4.5 g, 39.8 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 10 mL of 80% H₂SO₄. The procedure produced 4.6 g of the title materials. This mixture was separated into its components by chromatography to yield Isomer-A and Isomer-B.

EXAMPLE 141

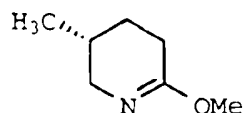
2,3,4,5-tetrahydro-6-methoxy-4R-methylpyridine



The Isomer-A product of EXAMPLE 140 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE

EXAMPLE 142

2,3,4,5-tetrahydro-6-methoxy-3R-methylpyridine



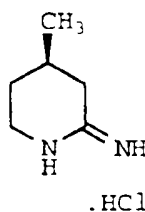
5

The Isomer-B product of EXAMPLE 140 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 143

4R-methylpiperidin-2-imine, monohydrochloride



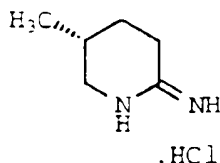
15

The product of EXAMPLE 141 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

20

EXAMPLE 144

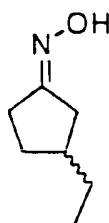
5R-methylpiperidin-2-imine, monohydrochloride



The product of EXAMPLE 142 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

EXAMPLE 145

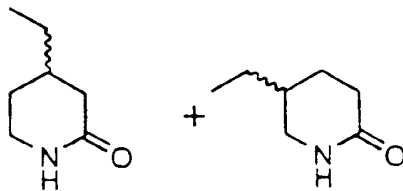
3-ethylcyclopentanone, oxime



A sample of 3-ethylcyclopentanone is converted to the title compound by the method of EXAMPLE 24 using hydroxylamine hydrochloride and NaOAc in a mixture of EtOH and water.

EXAMPLE 146

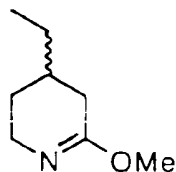
4-ethylpiperidin-2-one, mixture with 5-ethylpiperidin-2-one



The product of EXAMPLE 145 is converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 80% H₂SO₄. This product mixture is separated into its Isomer-A and Isomer-B components by chromatography.

EXAMPLE 147

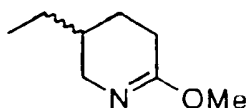
4-ethyl-2,3,4,5-tetrahydro-6-methoxypyridine



The Isomer-A product of EXAMPLE 146 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

EXAMPLE 148

3-ethyl-2,3,4,5-tetrahydro-6-methoxypyridine

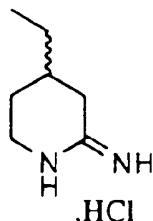


The Isomer-B product of EXAMPLE 146 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

100

EXAMPLE 149

4-ethylpiperidin-2-imine, monohydrochloride

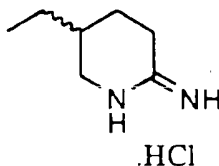


The product of EXAMPLE 147 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

10

EXAMPLE 150

5-ethylpiperidin-2-imine, monohydrochloride

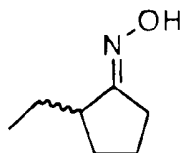


The product of EXAMPLE 148 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

20

EXAMPLE 151

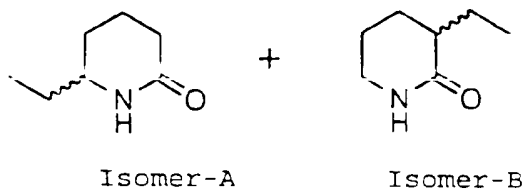
2-ethylcyclopentanone, oxime



A sample of 2-ethylcyclopentanone (F & B, 9.8 g, 87.5 mmol) was converted to the title compound by the method of EXAMPLE 24 using 8.5 g (122.5 mmol) of hydroxylamine hydrochloride and 12.9 g (157.5 mmol) of NaOAc in a mixture of 90 mL of EtOH and 90 mL of water. The procedure produced 12.0 g of the crude title compound as a yellow oil.

EXAMPLE 152

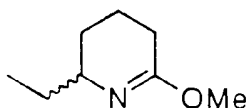
6-ethylpiperidin-2-one, mixture with 3-ethylpiperidin-2-one



The product of EXAMPLE 151 (2.1 g, 16.4 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 29 using 2.9 g (16.4 mmol) of benzene sulfonylchloride. The crude pale yellow solid product mixture (2.3 g) was separated into its Isomer-A and Isomer-B components by chromatography.

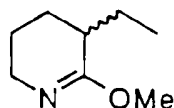
EXAMPLE 153

2-ethyl-2,3,4,5-tetrahydro-6-methoxypyridine



The Isomer-A product of EXAMPLE 152 (280 mg, 2.2 mmol) was reacted with trimethyloxonium tetrafluoroborate (425 mg, 2.9 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 300 mg (96%) of the title material as a

3-ethyl-3,4,5,6-tetrahydro-2-methoxypyridine



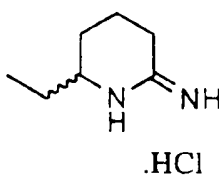
5

The Isomer-B product of EXAMPLE 152 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 155

6-ethylpiperidin-2-imine, monohydrochloride



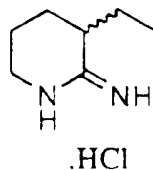
15

The product of EXAMPLE 153 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

20

EXAMPLE 156

3-ethylpiperidin-2-imine, monohydrochloride

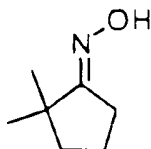


25

The product of EXAMPLE 154 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title

EXAMPLE 157

2,2-dimethylcyclopentanone, oxime



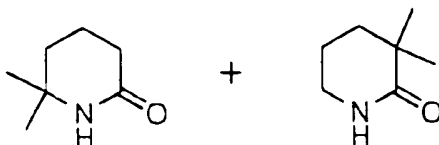
5

A sample of 2,2-dimethylcyclopentanone (Aldrich, 9.0 g, 80.0 mmol) was converted to the title compound by the method of EXAMPLE 24 using 7.8 g (112.0 mmol) of hydroxylamine hydrochloride and 11.8 g (144.0 mmol) of NaOAc in a mixture of 90 mL of EtOH and 90 mL of water. The procedure produced 13.1 g of the crude title compound as a colorless oil.

EXAMPLE 158

15

6,6-dimethylpiperidin-2-one, mixture with 3,3-dimethylpiperidin-2-one



20

Isomer-A

Isomer-B

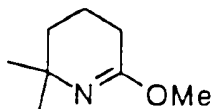
The product of EXAMPLE 157 (13.3 g, 104.7 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 29 using 18.5 g (104.7 mmol) of benzene sulfonylchloride. The crude pale yellow solid product mixture (8.3 g) was separated into its Isomer-A and Isomer-B components by chromatography.

EXAMPLE 159

2,3,4,5-tetrahydro-6-methoxy-2,2-dimethylpyridine

30

104

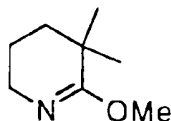


The Isomer-A product of EXAMPLE 158 (880 mg, 6.9 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.3 g, 9.0 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 502 mg (51%) of the title material as a pale yellow solid.

EXAMPLE 160

10

3,4,5,6-tetrahydro-2-methoxy-3,3-dimethylpyridine

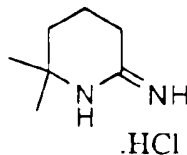


15 The Isomer-B product of EXAMPLE 158 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

EXAMPLE 161

20

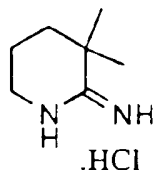
6,6-dimethylpiperidin-2-imine, monohydrochloride



25 The product of EXAMPLE 159 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

105

3,3-dimethylpiperidin-2-imine, monohydrochloride

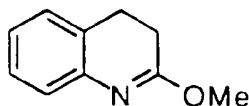


- 5 The product of EXAMPLE 160 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

EXAMPLE 163

10

3,4-dihydro-2-methoxyquinoline



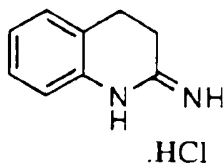
- 15 A sample of 3,4-dihydrocarbostyrl (Apin Chemicals Ltd., 736 mg, 5.0 mmol) was reacted with trimethyloxonium tetrafluoroborate (924 mg, 6.2 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 130 mg (16%) of the title material.

20

106

EXAMPLE 164

1,2,3,4-tetrahydroquinolin-2-imine, monohydrochloride



5

The product of EXAMPLE 163 (98 mg, 0.61 mmol) in 10 mL of MeOH and 10 mL of CH₂Cl₂ was reacted with ammonium chloride (27 mg, 0.52 mmol) by the method of EXAMPLE 27 to yield 57 mg (47%) of the title material.

HRMS m/z M⁺ 147.086; C₉H₁₁N₂ requires 147.092.

IR (KBr): ¹H NMR(D₂O): δ 7.37-7.30 (m, 2H), 7.25 (m, 1H), 7.10 (m, 1H), 3.00 (m, 2H), 2.93 (m, 2H).

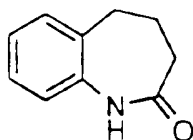
15

Elemental analysis: C₉H₁₀N₂ · 1.0 HCl · 0.2 H₂O · 1.0 NH₄Cl (MW = 240.65)

	C	H	N	Cl
20 Calculated:	44.92	6.49	17.46	29.46
Found:	44.94	6.48	17.58	29.60

EXAMPLE 165

25 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one



A sample of alpha tetralone (Aldrich, 36.5 g, 0.25 mol) was converted to the title material by the method of EXAMPLE 50

30

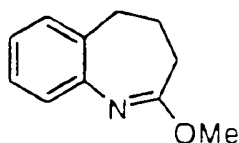
107

yielded after recrystallization from EtOH 12.1 g (30%) of the title product.

EXAMPLE 166

5

4,5-dihydro-2-methoxy-3H-1-benzazepine

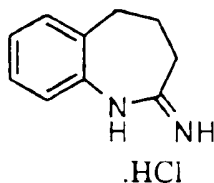


10 A sample of the title compound of EXAMPLE 165 (3.2 g, 20.0 mmol) was reacted with trimethyloxonium tetrafluoroborate (4.4 g, 30.0 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 2.5 g (73%) of the title material.

15

EXAMPLE 167

2,3,4,5-tetrahydro-1H-1-benzazepin-2-imine,
monohydrochloride



20

The product of EXAMPLE 166 (1.9 g, 11.1 mmol) in 15 mL of MeOH and 10 mL of CH₂Cl₂ was reacted with ammonium chloride (413 mg, 7.8 mmol) by the method of EXAMPLE 27 to yield 1.4 g (88%) of the title material.

HRMS m/z M⁺ 161.103; C₁₀H₁₃N₂ requires 161.108.

¹H NMR(D₂O): δ 7.44-7.32 (m, 3H), 7.2 (m, 1H), 2.81 (m, 2H), 2.50 (m, 2H), 2.34 (m, 2H).

108

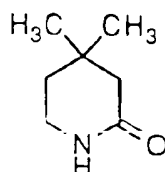
(MW = 202.63)

	C	H	N	Cl
Calculated:	59.28	6.80	14.24	17.50
5 Found:	59.30	6.68	13.90	17.41

EXAMPLE 168

4,4-dimethylpiperidin-2-one

10



A solution of 3,3-dimethylglutaric anhydride (10 g, 70 mmol) in ammonium hydroxide (conc., 30 mL) was hydrogenated over
15 Pd/Al₂O₃ at 1600 psi and 250 °C for 3 h. The flask was cooled to RT and treated with brine (satd., 75 mL) followed by extraction with CH₂Cl₂ (150 mL), dried (Na₂SO₄) and evaporated to yield a solid, that was purified by chromatography to yield 1.4 g (16%) of the title material.

20

IR (KBr): 3260, 2949, 1655, 1626, 1502, 1338

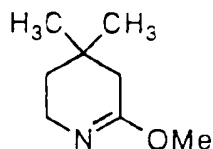
¹H NMR(CDCl₃): δ 5.98 (br s, 1H), 3.38-3.32 (m, 2H), 2.13 (s, 2H), 1.59 (t, J = 5 Hz, 2H), 1.05 (s, 6 H)Elemental analysis: C₇H₁₃NO · 0.02 CHCl₃ (MW = 127.19)

25

	C	H	N
Calculated:	65.07	10.13	10.81
Found:	65.20	9.74	10.78

EXAMPLE 169

2,3,4,5-tetrahydro-4,4-dimethyl-6-methoxypyridine



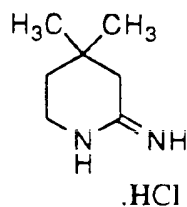
5

A sample of the title compound of EXAMPLE 168 (636 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (890 mg, 6 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 550 mg (78%) of the title material.

EXAMPLE 170

4,4-dimethylpiperidin-2-imine, monohydrochloride

15



The product of EXAMPLE 169 (550 mg, 3.9 mmol) in 25 mL of MeOH was reacted with ammonium chloride (178 mg, 3.3 mmol) by the method of EXAMPLE 27 to yield 460 mg (86%) of the title material.

DSC: 167.65 °C; MS (EI): m/e, 126 (100 %, M⁺).
IR (KBr): 3294, 3148, 3009, 2945, 1687; ¹H NMR(DMSO d₆-D₂O exchange): δ 3.33 (t, J = 5 Hz, 2H), 2.34 (s, 2H), 1.60 (t, J = 5 Hz, 2H), 1.00 (s, 6 H)

Elemental analysis: C₇H₁₄N₂ . 1.0 HCl . 0.2 H₂O . 0.2 NH₄Cl (MW = 176.97)

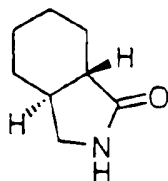
110

	C	H	N	Cl
Calculated:	47.51	9.23	17.41	24.04
Found:	47.13	9.05	17.76	24.31

5

EXAMPLE 171

(trans)-octahydro-1H-isoindol-1-one



10

A solution of *trans*-1,2-cyclohexanedicarboxylic anhydride (10 g, 65 mmol) in ammonium hydroxide (conc., 30 mL) was hydrogenated by the method of EXAMPLE 168 to yield 7.4 g (80%) of the title material.

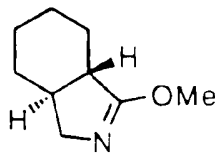
15

mp: 85-88 °C; ¹H NMR(CDCl₃): δ 6.47 (br s, 1H), 3.42-3.31 (m, 1H), 3.00-2.93 (m, 1H), 2.50-2.35 (m, 1H), 2.07-1.15 (m, 9H).

EXAMPLE 172

20

(trans)-3a,4,5,6,7,7a-hexahydro-3-methoxy-1H-isoindole

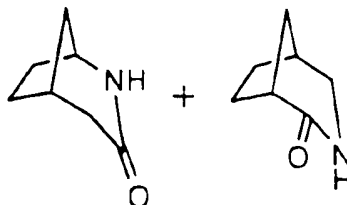


25

A sample of the title compound of EXAMPLE 171 (1.39 g, 10 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.78 g, 12 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 1.05 g (69%) of the title material.

EXAMPLE 175

2-azabicyclo[3.2.1]octan-3-one, mixture with 3-
5 azabicyclo[3.2.1]octan-2-one



Isomer-A

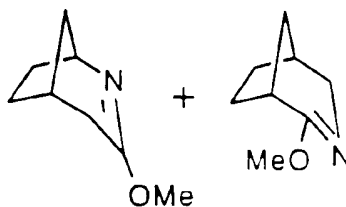
Isomer-B

10

The product of EXAMPLE 174 (10 g, 80 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 25 using 80% H₂SO₄. This product mixture was purified by chromatography but not separated into its
15 Isomer-A and Isomer-B components to yield 835 mg (8%), as a clear liquid.

EXAMPLE 176

20 3-methoxy-2-azabicyclo[3.2.1]oct-2-ene, mixture with 2-methoxy-3-azabicyclo[3.2.1]oct-2-ene

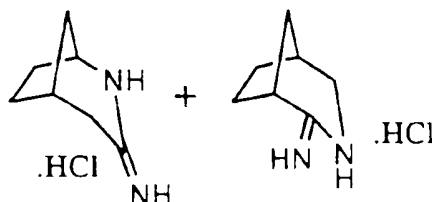


25 A sample of the title compounds of EXAMPLE 175 (650 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (890 g, 6 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 550 mg (80%) of the title materials.

EXAMPLE 177

2-azabicyclo[3.2.1]octan-3-imine, monohydrochloride, mixture
with 3-azabicyclo[3.2.1]octan-2-imine, monohydrochloride

5



The products of EXAMPLE 176 (530 mg, 3.9 mmol) in 25 mL of
MeOH were reacted with ammonium chloride (178 mg, 3.3 mmol)
10 by the method of EXAMPLE 27 to yield 400 mg (67%) of the
title materials.

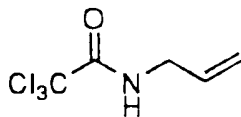
MS (EI) m/e; 124 (90 %, M⁺), 83 (100 %)

¹H NMR(DMSO d₆-D₂O exchange): δ 3.44-3.37 (m, 1H), 3.19-3.11 (m,
15 1H), 2.95-2.89 (m, 1H), 2.57-2.50 (m, 2H), 2.07- 1.52 (m, 5H).
Elemental analysis: C₈H₁₄N₂ · 1.08 HCl · 0.75 H₂O · 0.4
NH₄Cl (MW = 212.500)

	C	H	N	Cl
20 Calculated:	42.36	8.22	16.94	26.44
Found:	42.70	8.27	17.03	26.65

EXAMPLE 178

25 2,2,2-trichloro-N-(2-propenyl)acetamide



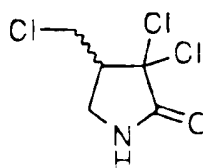
To a stirred solution of allylamine (5 g, 88 mmol) and
30 triethylamine (9.6 g, 95 mmol) in CH₂Cl₂ (200 mL) at -10 °C

resulting solution was allowed to gradually warm to RT and stir for 24 h. The reaction solution was extracted with brine (satd., 100 mL) and dried (Na_2SO_4) to yield 17 g (96%) of the title compound as a white solid.

5

EXAMPLE 179

3,3-dichloro-4-(chloromethyl)pyrrolidin-2-one



10

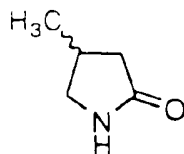
To a stirred solution of the title compound EXAMPLE 178 (15 g, 74 mmol) in xylene (600 mL) under N_2 was added $\text{RuCl}_2(\text{PPh}_3)_3$ (696 mg (0.74 mmol)), and the solution was refluxed for 2 h. The solvent was removed and the residue was chromatographed and crystallized (EtOAc) to yield 4.5 g (30%) of the title compound as a solid.

^1H NMR(CDCl_3): δ 7.40 (br s, 1H), 4.00 (dd, J = 4, 12 Hz, 1H), 3.76 (dd, J = 9, 12 Hz, 1H), 3.70 (dd, J = 6, 8 Hz, 1H), 3.28 (dd, J = 8, 9 Hz, 1H), 3.12-3.23 (m, 1 H).

20

EXAMPLE 180

4-methylpyrrolidin-2-one

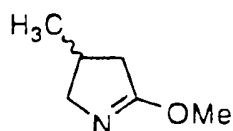


A mixture of the title compound in EXAMPLE 179 (3 g, 15 mmol), tributyltin hydride (14.3 mL) and AIBN (25 mg) was

30

EXAMPLE 181

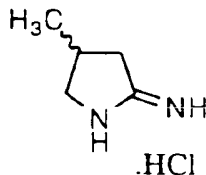
3,4-dihydro-5-methoxy-3-methyl-2H-pyrrole
5



The product of EXAMPLE 180 (500 mg, 5 mmol) was reacted with trimethyloxonium tetrafluoroborate (890 mg, 6 mmol) by the
10 method of EXAMPLE 26 to yield, after chromatography 610 mg of the title material containing traces of solvent.

EXAMPLE 182

15 4-methylpyrrolidin-2-imine, monohydrochloride



The product of EXAMPLE 181 (610 mg, 5 mmol) in 25 mL of MeOH
20 was reacted with ammonium chloride (200 mg, 4 mmol) by the method of EXAMPLE 27 to yield 500 mg (70 %) of the title material.

HRMS m/z M⁺ 98.0844; C₅H₁₀N₂ requires 98.0844.

25

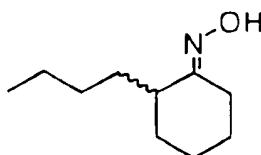
Elemental analysis: C₅H₁₀N₂ · HCl · 0.25 H₂O · 0.75 NH₄Cl (MW = 179.23)

	C	H	N	Cl
Calculated:	33.50	8.15	21.49	34.62
30 Found:	33.17	7.96	21.40	34.69

116

EXAMPLE 183

2-butylcyclohexanone, oxime



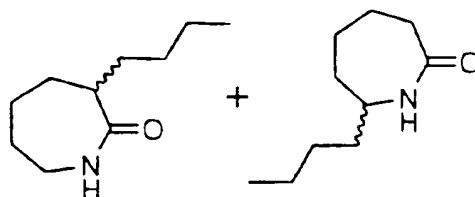
5

A sample of 2-n-butylcyclohexanone (Aldrich, 10.4 g, 67.2 mmol) was converted to the title compound by the method of EXAMPLE 24 using 7.0 g (100.7 mmol) of hydroxylamine hydrochloride and 9.8 g (120.1 mmol) of NaOAc in a mixture of 75 mL of EtOH and 50 mL of water. The procedure produced 11.3 g (99%) of the crude title compound.

EXAMPLE 184

15

3-butylhexahydro-1H-azepin-2-one, mixture with 7-butylhexahydro-1H-azepin-2-one



Isomer-A

Isomer-B

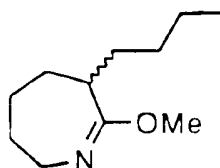
20

The product of EXAMPLE 184 (11.1 g, 65.6 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 29 using 12.3 g (70.0 mmol) of benzene sulfonylchloride. The crude pale yellow solid product mixture (8.3 g) was separated into its Isomer-A and Isomer-B components by chromatography.

EXAMPLE 185

117

6-butyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

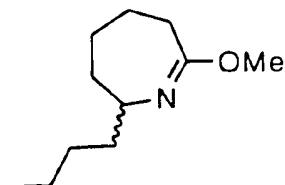


- 5 The Isomer-A product of EXAMPLE 184 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

EXAMPLE 186

10

2-butyl-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



- 15 The Isomer-B product of EXAMPLE 184 (0.63 g, 3.7 mmol) was reacted with trimethyloxonium tetrafluoroborate (0.71 g, 4.8 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 0.53 g (84%) of the title material.

- 20 Elemental analysis: $C_{11}H_{21}NO \cdot 0.125 H_2O$ (MW = 185.55)

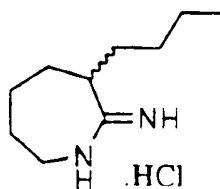
	C	H	N
Calculated:	71.21	11.54	7.55
Found:	71.14	11.73	7.25

25

EXAMPLE 187

3-butylhexahydro-1H-azepin-2-imine, monohydrochloride

118

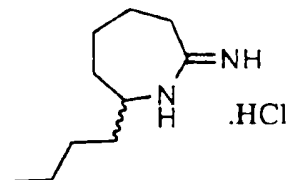


The product of EXAMPLE 185 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

EXAMPLE 188

7-butylhexahydro-1H-azepin-2-imine, monohydrochloride

10



The product of EXAMPLE 186 (500 mg, 2.7 mmol) in 20 mL of MeOH was reacted with ammonium chloride (124 mg, 2.3 mmol) by the method of EXAMPLE 27 to yield 425 mg (74%) of the title material.

^1H NMR (400 MHz, CD_3OD) δ 3.64-3.55 (m, 1H), 2.79 (ddd, 1H, $J=14.6, 6.7, 1.5$ Hz), 2.61 (ddt, 1H, $J=14.6, 6.7, 1.5$ Hz), 2.06-1.95 (m, 2H), 1.90-1.81 (m, 1H), 1.76-1.55 (m, 3H), 1.55-1.31 (m, 6H), 0.95 (t, 3H, $J = 7.1$ Hz).

Elemental analysis: $\text{C}_{10}\text{H}_{20}\text{N}_2 \cdot 1.0 \text{ HCl} \cdot 0.33 \text{ H}_2\text{O} \cdot 0.03 \text{ NH}_4\text{Cl}$ (MW = 212.29)

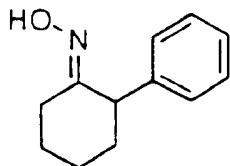
25

	C	H	N	Cl
Calculated:	56.58	10.34	13.39	17.20
Found:	56.49	10.47	12.99	17.55

119

EXAMPLE 189

2-phenylcyclohexanone, oxime



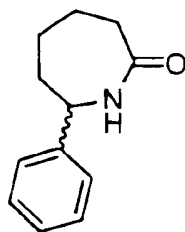
5

A sample of 2-phenylcyclohexanone (Aldrich, 10.4 g, 60 mmol) was converted to the title compound by the method of EXAMPLE 24 using 7.2 g (104 mmol) of hydroxylamine hydrochloride and 8.4 g (102 mmol) of NaOAc in a mixture of 75 mL of EtOH and 75 mL of water. The procedure produced 11.0 g (97%) of the title material as a white solid.

15

EXAMPLE 190

hexahydro-7-phenyl-1H-azepin-2-one



20

To the product of EXAMPLE 189 (10.9 g, 57.7 mmol) in 60 mL of acetone was added 1N NaOH (64 mL, 64 mmol). After cooling this mixture in an ice bath, benzene sulfonylchloride (10.6 g, 60 mmol) was added drop-wise over 5 minutes to the stirred reaction mixture maintained under a N₂ atmosphere. The reaction was allowed to warm to room temperature and stir overnight. The filtrate was concentrated and partitioned between EtOAc and brine. The

25

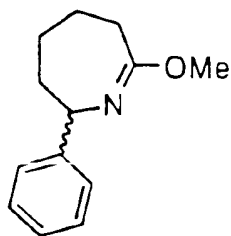
120

of all solvent under reduced pressure. A white solid was thus obtained and recrystallized from hot methyl t-butyl ether / acetone to yield 3.5 g (32%) of the title material.

5

EXAMPLE 191

3,4,5,6-tetrahydro-7-methoxy-2-phenyl-2H-azepine



10

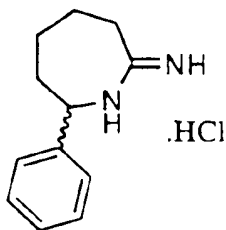
The product of EXAMPLE 29 (1.75 g, 9.3 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.8 g, 12.0 mmol) by the method of EXAMPLE 26 to yield 1.4 g (72%) of the title material.

15

EXAMPLE 192

hexahydro-7-phenyl-1H-azepin-2-imine, monohydrochloride

20



The product of EXAMPLE 191 (1.4 g, 6.9 mmol) in 75 mL of MeOH was reacted with ammonium chloride (0.31 g, 5.9 mmol) by the method of EXAMPLE 27 to yield 1.2 g (77%) of the title material.

25

121

^1H NMR(CD_3OD): δ 7.50-7.30 (m, 5H), 2.98 (tt, 1H), 2.74 (dd, 1H), 2.12-1.76 (m, 6H), 1.60 (m, 1H).

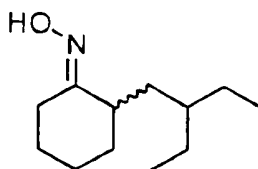
Elemental analysis: $\text{C}_{12}\text{H}_{16}\text{N}_2 \cdot \text{HCl} \cdot 0.5 \text{H}_2\text{O}$ (MW =
5 233.74)

	C	H	N	Cl
Calculated:	61.66	7.76	11.98	15.17
Found:	61.69	8.15	11.42	15.41

10

EXAMPLE 193

2-(2-ethylbutyl)cyclohexanone, oxime



15

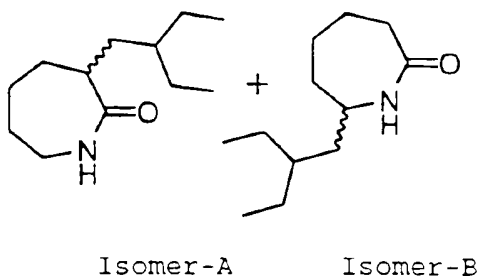
A sample of 2-(2-ethyl)butylcyclohexanone (Aldrich, 10.1 g, 55.5 mmol) was converted to the title compound by the method of EXAMPLE 24 using 5.4 g (77.7 mmol) of
20 hydroxylamine hydrochloride and 8.2 g (99.9 mmol) of NaOAc in a mixture of 90 mL of EtOH and 90 mL of water. The procedure produced 11.9 g (100%) of the crude title compound.

122

EXAMPLE 194

3-(2-ethylbutyl)hexahydro-1H-azepin-2-one, mixture with 7-(2-ethylbutyl)hexahydro-1H-azepin-2-one

5

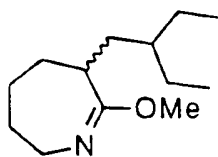


The product of EXAMPLE 193 (7.3 g, 37.1 mmol) was converted to the title compound mixture of two regioisomers by the method of EXAMPLE 29 using 7.1 g (40.0 mmol) of benzene sulfonylchloride. The crude pale yellow oil product mixture (7.3 g) was separated into its Isomer-A and Isomer-B components by chromatography.

15

EXAMPLE 195

6-(2-ethylbutyl)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



20

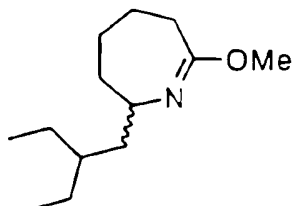
The Isomer-A product of EXAMPLE 194 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

25

123

EXAMPLE 196

2-(2-ethylbutyl)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

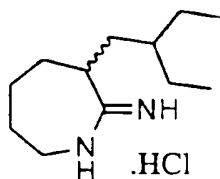


5

The Isomer-B product of EXAMPLE 194 (520 mg, 2.6 mmol) was reacted with trimethyloxonium tetrafluoroborate (506 mg, 3.4 mmol) by the method of EXAMPLE 26 to yield, after chromatography, 472 mg (85%) of the title material.

EXAMPLE 197

3-(2-ethylbutyl)hexahydro-1H-azepin-2-imine,
monohydrochloride

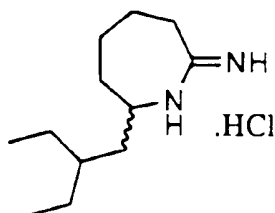


The product of EXAMPLE 195 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

EXAMPLE 198

7-(2-ethylbutyl)hexahydro-1H-azepin-2-imine,
monohydrochloride

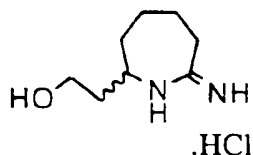
5



The product of EXAMPLE 196 (470 mg, 2.2 mmol) in 18 mL of
MeOH was reacted with ammonium chloride (98 mg, 1.8 mmol)
10 by the method of EXAMPLE 27 to yield 242 mg of the title
material.

EXAMPLE 199

15 hexahydro-7-imino-1H-azepine-2-ethanol, monohydrochloride



Hexahydro-7-(2-propenyl)-1H-azepin-2-imine,
20 monohydrochloride (the product of EXAMPLE 108) (3.0 g,
14.7 mmol) is dissolved in a mixture of methylene chloride
(100 mL) and methanol (50 mL) and cooled to -78° C. Ozone
is then bubbled through until a blue color is observed.
The reaction is flushed with N₂ to remove excess ozone.
25 The reaction mixture is warmed to room temperature and
concentrated in vacuo to a residue. The residue is
dissolved in ethanol (100 mL), cooled to 0° C, and
vigorously stirred as a cold solution of sodium

125

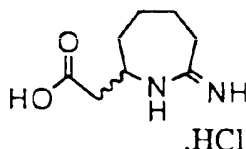
the concomitant addition of 2 M acetic acid in water, maintaining the pH (pH paper) at 8 to 9. After the addition is complete, the mixture is stirred at room temperature for 10 hr, the reaction mixture is acidified to pH 2 with dilute HCl, and the reaction mixture is concentrated *in vacuo* to a gum. The gum is dissolved in a small amount of ethanol, filtered, evaporated *in vacuo* to a solid, dissolved in water and applied to an ion exchange column of Dowex 50 (H⁺). The column is washed with deionized water, and the title compound eluted with 2 N HCl. The eluate is concentrated *in vacuo* to a solid, dissolved in a small amount of water, filtered, and lyophilized to give the title compound. C₈H₁₆N₂O.HCl
mw=192.69

15

EXAMPLE 200

hexahydro-7-imino-1H-azepine-2-acetic acid,
monohydrochloride

20



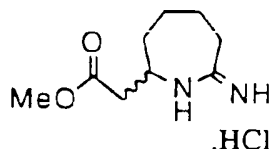
Hexahydro-7-(2-propenyl)-1H-azepin-2-imine, monohydrochloride (the product of EXAMPLE 108) (3.0 g, 14.7 mmol) is dissolved in methyl ethyl ketone (150 mL) and cooled to -78° C. Ozone is then bubbled through until a blue color is observed. A 10% solution of H₂O₂ (12 mL) is added at -78° C. The reaction mixture is allowed to warm to room temperature and concentrated *in vacuo* to a solid. The solid is triturated with diethyl ether, dried, dissolved in water, and lyophilized to give title compound. if purification is necessary, it is effected by dissolving the material in deionized water, and passing

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rapidly with 1 N ammonium hydroxide. The solution is rapidly evaporated in vacuo at room temperature, and taken up in water. The pH is adjusted to 6.2 with 1 N HCl. The solution is concentrated in vacuo to a solid, the title compound. $C_8H_{14}N_2O_2 \cdot HCl$ mw=206.67

EXAMPLE 201

methyl hexhydro-7-imino-1H-azepine-2-acetate,
10 monohydrochloride

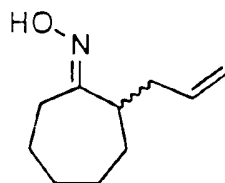


Thionyl chloride (3.5 g, 30 mmol) is added carefully and slowly to a stirring volume of dry cold (-20°C) methanol (150 mL). After addition is complete, the solution is stirred at -20 °C for 30 min. The title product of EXAMPLE 200 (3.0 g, 14.6 mmol) is dissolved in the minimum of dry methanol and treated with 3A molecular sieves. The mixture is filtered protected from moisture, and added to the cold methanolic HCl solution. The reaction mixture is protected from moisture and allowed to stir at room temperature overnight. The reaction mixture is concentrated in vacuo to give the title product.

$C_9H_{16}N_2O_2 \cdot HCl$ mw=220.81

EXAMPLE 202

2-(2-propenyl)cycloheptanone, oxime



5

2-carboethoxycycloheptanone (1 mmol), finely powdered potassium carbonate (2 mmol), allyl bromide (1.5 mmol), and tetrabutyl ammonium iodide (10 mg/mmol) are combined in dry DMF (1.25 mL/mmol) and stirred under N₂ at 55 to 60 °C for 16 to 18 hours. The room temperature reaction mixture is poured into water and extracted with Et₂O and EtOAc. The combined organics are washed with brine, dried, and stripped of all solvent under reduced pressure to provide 2-allyl-2-carboethoxycycloheptanone. This material is combined with lithium chloride (5 mmol), water (1.05 mmol) and dimethyl sulfoxide (5 mL/mmol) and the mixture refluxed for approximately 4 hrs. The mixture is poured into water and extracted with Et₂O and EtOAc. The combined organics are washed with brine, dried, and stripped of all solvent under reduced pressure to provide 2-allylcycloheptanone. A sample of the 2-allylcycloheptanone is converted to the title compound by the method of EXAMPLE 24 using hydroxylamine hydrochloride and NaOAc in a mixture of EtOH and water.

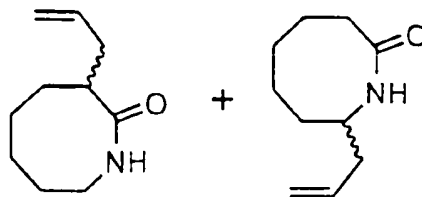
20

25

EXAMPLE 203

octahydro-3-(2-propenyl)azocin-2-one, mixture with
octahydro-8-(2-propenyl)azocin-2-one

5

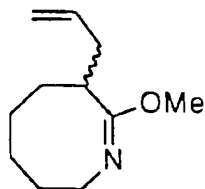


The product of EXAMPLE 202 is converted to the title
compound mixture of two regioisomers by the method of
10 EXAMPLE 29 using benzene sulfonylchloride. The crude
product mixture is separated into its Isomer-A and Isomer-
B components by chromatography.

EXAMPLE 204

15

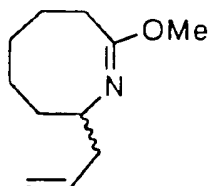
3,4,5,6,7,8-hexahydro-2-methoxy-3-(2-propenyl)azocine



20 The Isomer-A product of EXAMPLE 203 is reacted with
trimethyloxonium tetrafluoroborate by the method of
EXAMPLE 26 to produce the title material.

EXAMPLE 205

2,3,4,5,6,7-hexahydro-8-methoxy-2-(2-propenyl)azocine



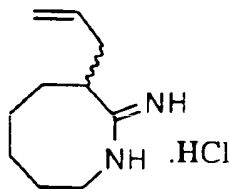
5

The Isomer-B product of EXAMPLE 203 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

10

EXAMPLE 206

octahydro-3-(2-propenyl)azocin-2-imine, monohydrochloride



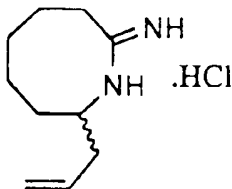
15

The product of EXAMPLE 204 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

20

EXAMPLE 207

octahydro-3-(2-propenyl)azocin-2-imine, monohydrochloride



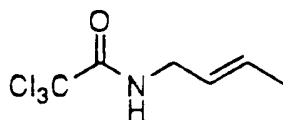
130

The product of EXAMPLE 205 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

5

EXAMPLE 208

N-(2-butenyl)-2,2,2-trichloroacetamide



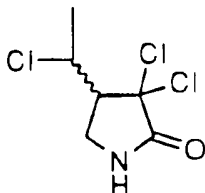
10

A solution of 3 butene 2 ol (8.7 mL, 100 mmol) in THF (50 mL) was added to potassium hydride (KH, 600 mg, 15 mmol) over 15 min. The resulting alkoxide solution was added to a stirred solution of trichloroacetonitrile (10.03 mL, 100 mmol) in ether (100 mL) at -10 °C. The solution was stirred at 0 °C for 3 h, followed by removal of solvent under reduced pressure (temperature <25 °C); pentane (400 mL) and methanol (1 mL) were added, and the mixture filtered. Concentration afforded a yellow oil (17.4 g). The oil was dissolved in xylene (450 mL) and refluxed for 2.5 h. The solvent was removed to yield 16.8 g of the title compound as a white solid.

25

EXAMPLE 209

3,3-dichloro-4-(1-chloroethyl)pyrrolidin-2-one



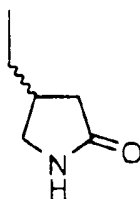
A mixture of the title compound in EXAMPLE 208 was treated

131

EXAMPLE 210

4-ethylpyrrolidin-2-one

5

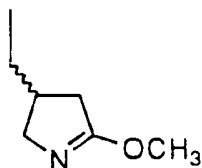


A mixture of the title compound in EXAMPLE 209 was treated with tributyltin hydride and AIBN by the method of EXAMPLE 180 to produce the title material.

EXAMPLE 211

3-ethyl-3,4-dihydro-5-methoxy-2H-pyrrole

15

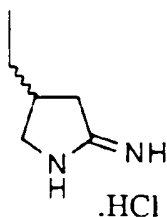


The product of EXAMPLE 180 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

132

EXAMPLE 212

4-ethylpyrrolidin-2-imine, monohydrochloride

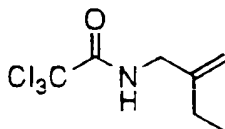


The product of EXAMPLE 211 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

10

EXAMPLE 213

2,2,2-trichloro-N-(2-methylenebutyl)acetamide



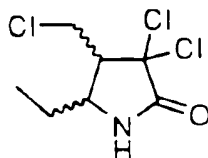
Cis-2-pentene-1-cl was treated with NaH and trichloroacetonitrile followed by work up and treatment in refluxing xylene by the method of EXAMPLE 208 to produce the material.

20

EXAMPLE 214

3,3-dichloro-4-(chloromethyl)-5-ethyl-pyrrolidin-2-one

25



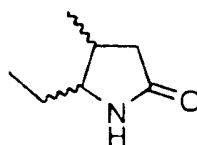
133

A mixture of the title compound in EXAMPLE 213 was treated with $\text{RuCl}_2(\text{PPh}_3)_3$ in refluxing xylene by the method of EXAMPLE 179 to produce the title material.

5

EXAMPLE 215

5-ethyl-4-methylpyrrolidin-2-one



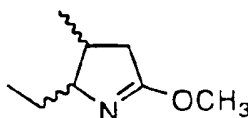
10

A mixture of the title compound in EXAMPLE 214 was treated with tributyltin hydride and AIBN by the method of EXAMPLE 180 to produce the title material.

15

EXAMPLE 216

2-ethyl-3,4-dihydro-5-methoxy-3-methyl-2H-pyrrole



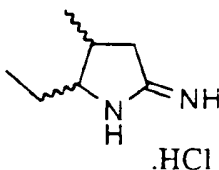
20

The product of EXAMPLE 215 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

134

EXAMPLE 217

5-ethyl-4-methylpyrrolidin-2-imine, monohydrochloride



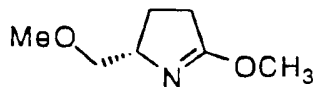
5

The product of EXAMPLE 216 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

10

EXAMPLE 218

3,4-dihydro-5-methoxy-2S-(methoxymethyl)-2H-pyrrole



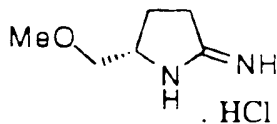
15

S-(+)-5-(hydroxymethyl)-2-pyrrolidinone is reacted with trimethyloxonium tetrafluoroborate (2.2 equivalents) by the method of EXAMPLE 26 to produce the title material.

20

EXAMPLE 219

5S-(methoxymethyl)pyrrolidin-2-imine, monohydrochloride



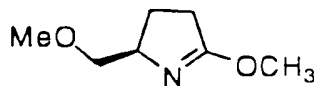
25

The product of EXAMPLE 218 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate

135

EXAMPLE 220

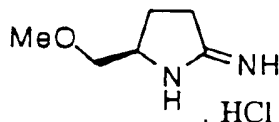
3,4-dihydro-5-methoxy-2R-(methoxymethyl)-2H-pyrrole



R-(-)-5-(hydroxymethyl)-2-pyrrolidinone is reacted with trimethyloxonium tetrafluoroborate (2.2 equivalents) by the method of EXAMPLE 26 to produce the title material.

EXAMPLE 221

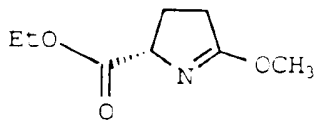
5R-(methoxymethyl)pyrrolidin-2-imine, monohydrochloride



The product of EXAMPLE 220 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

EXAMPLE 222

ethyl 3,4-dihydro-5-methoxy-2H-pyrrole-2S-carboxylate

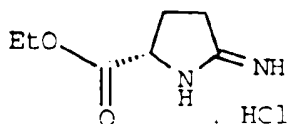


Ethyl (S)-(+)-2-pyrrolidinone-5-carboxylate is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

136

EXAMPLE 223

ethyl 5-iminopyrrolidine-2S-carboxylate, monohydrochloride

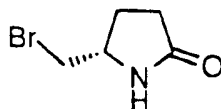


The product of EXAMPLE 222 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

10

EXAMPLE 224

5S-(bromomethyl)pyrrolidin-2-one



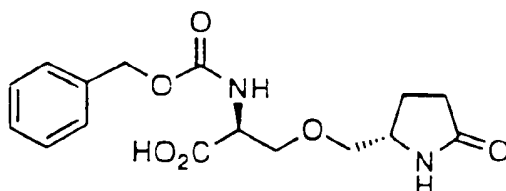
A solution of S-(+)-5-(hydroxymethyl)-2-pyrrolidinone (2 g, 17.4 mmol) in CH₂Cl₂ (160 mL) was treated with triphenylphosphine (10.5 g, 40 mmol) and carbontetrabromide (13.25 g, 40 mmol). The resulting solution was stirred for 18 h followed by concentration and chromatography (40:1 EtOAc/hexane, silica gel) to yield 1.32g of the title compound as a white solid.

20

EXAMPLE 225

3-[[[(5-oxopyrrolidin-2S-yl)methyl]oxy]-2S-
[[[(phenylmethoxy)carbonyl]amino]propanoic acid

5



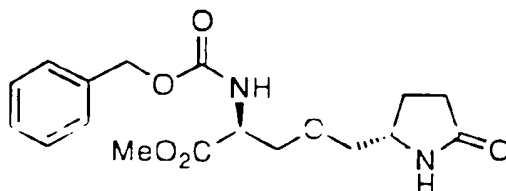
A solution of N- α -Cbz-serine in DMF is treated with 2
equivalents of NaH at 0 °C, followed by the addition of
10 the title compound of EXAMPLE 224. The resulting solution
is stirred for 5 h at RT, water is added and the mixture
extracted with EtOAc. The solution is acidified to pH 3.5
with citric acid and extracted with EtOAc, dried and
concentrated to yield the title compound.

15

EXAMPLE 226

methyl 3-[[[(5-oxopyrrolidin-2S-yl)methyl]oxy]-2S-
[[[(phenylmethoxy)carbonyl]amino]propanoate

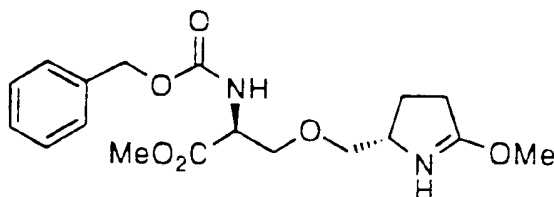
20



The product of EXAMPLE 225 in DMF is treated with cesium
carbonate followed by methyl iodide. The resulting
25 mixture is filtered then partitioned between EtOAc and
water. The organic phase is washed with brine, dried and
concentrated to yield the title compound.

EXAMPLE 227

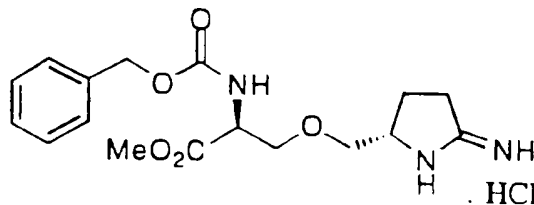
methyl 3-[[(3,4-dihydro-5-methoxy-2H-pyrrolidin-2S-yl)methyl]oxy]-2S-[[(phenylmethoxy) carbonyl]
 5 amino]propanoate



The product of EXAMPLE 226 is reacted with
 10 trimethyloxonium tetrafluoroborate by the method of
 EXAMPLE 26 to produce the title material.

EXAMPLE 228

15 methyl 3-[[(5-iminopyrrolidin-2S-yl)methyl]oxy]-2S-
 [[(phenylmethoxy) carbonyl]amino]propanoate,
 monohydrochloride



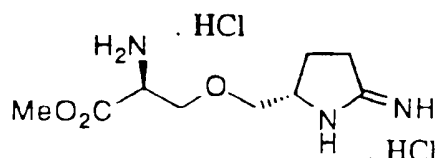
20

The product of EXAMPLE 227 in MeOH is reacted with
 ammonium chloride by the method of EXAMPLE 27 to generate
 the title material.

139

EXAMPLE 229

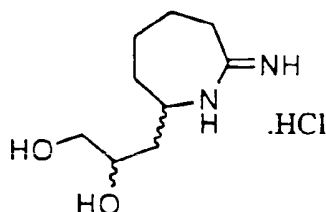
5 methyl 2S-amino-3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]propanoate, dihydrochloride



10 The product of EXAMPLE 228 in MeOH/HCl is reacted with H₂ over Pd/C 10% to generate the title material.

EXAMPLE 230

3-(7-iminoazepin-2-yl)-1,2-propanediol, monohydrochloride



15

To the product of EXAMPLE 108 in a mixture of acetone and THF is added osmium tetroxide. An aqueous solution of morpholine N-oxide is then added to the reaction and the mixture is stirred at room temperature over night. Sodium bisulfite is then added and this mixture is evaporated in vacuo to a solid. The solid is extracted with methanol thrice, and the combined extracts are evaporated in vacuo to a solid. This solid is dissolved in water and applied to a Dowex-50 ion exchange column (H⁺), which is eluted with water and then 0.2 N HCl to yield the title compound.

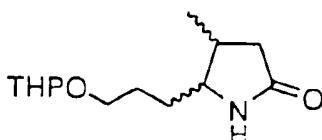
141

A mixture of the title compound in EXAMPLE 232 is treated with $\text{RuCl}_2(\text{PPh}_3)_3$ in refluxing xylene by the method of EXAMPLE 179 to produce the material.

5

EXAMPLE 234

4-methyl-5-[3-[(tetrahydropyran-2-yl)oxy]propyl]pyrrolidin-2-one



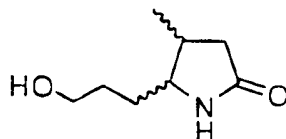
10

A mixture of the title compound in EXAMPLE 233 is treated with tributyltin hydride and AIBN by the method of EXAMPLE 180 to produce the title product.

15

EXAMPLE 235

5-(3-hydroxypropyl)-4-methylpyrrolidin-2-one



20

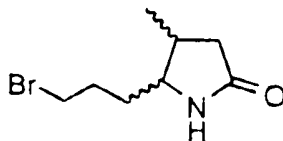
A mixture of the title compound of EXAMPLE 234 is treated with acetic acid : THF : water (4:2:1), and concentrated. The resulting material is purified by column chromatography to yield the title material.

25

142

EXAMPLE 236

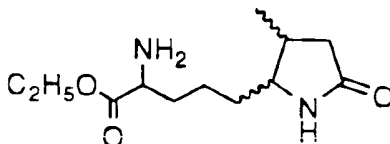
5-(3-bromopropyl)-4-methylpyrrolidin-2-one



5

A mixture of the title compound of EXAMPLE 235 is treated with triphenylphosphine and carbon tetrabromide by the method of EXAMPLE 224 to generate the title material.

10

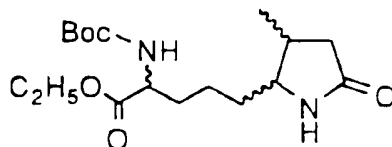
EXAMPLE 237ethyl α -amino-3-methyl-5-oxopyrrolidine-2-pentanoate

15

A solution of *N*-(diphenylmethylene)glycine ethyl ester (Aldrich, 37 mmol) in THF (20 mL) is added to -72 °C solution of sodium bis (trimethylsilylamide) (35 mmol, 0.5 M in THF), while the solution is kept below -65 °C. The resulting solution is then stirred at -72 °C for 30 min.; followed by the rapid addition of a cooled solution (-72 °C) of the product from EXAMPLE 236 (24 mmol) in THF via canula. The cooling bath is removed immediately and the mixture allowed to warm to 0 °C for 4 h. The reaction mixture is partitioned between ether and 10% aqueous sodium bisulfate, then dried and concentrated. The product is purified by column chromatography. This intermediate is then treated with 0.1 N aqueous

EXAMPLE 238

ethyl α -[[(1,1-dimethylethoxy)carbonyl]amino]-3-methyl-5-oxopyrrolidine-2-pentanoate

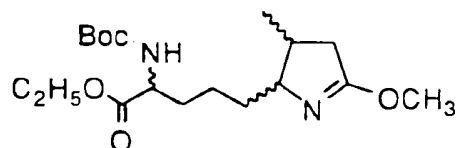


A solution of compound in EXAMPLE 237 is treated with di-
t butyldicarbonate in dichloromethane with triethylamine
present. The reaction mixture is extracted with water,
dried (MgSO₄), filtered and stripped to afford the title
compound.

15

EXAMPLE 239

ethyl α -[[(1,1-dimethylethoxy)carbonyl]amino]-3,4-dihydro-5-methoxy-3-methylpyrrolidine-2-pentanoate



20

The product of EXAMPLE 238 is reacted with
trimethyloxonium tetrafluoroborate by the method of
EXAMPLE 26 to produce the title material.

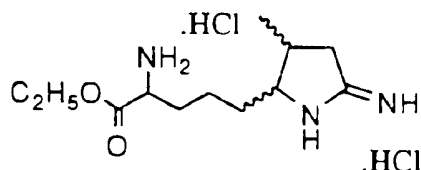
25

144

EXAMPLE 240

ethyl α -amino-5-imino-3-methylpyrrolidine-2-pentanoate,
dihydrochloride

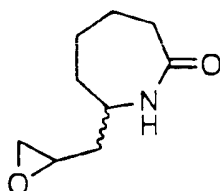
5



The product of EXAMPLE 239 in MeOH is reacted with
ammonium chloride by the method of EXAMPLE 27. This
10 material is then treated with 3M HCl/ethyl acetate to
generate the title material.

EXAMPLE 241

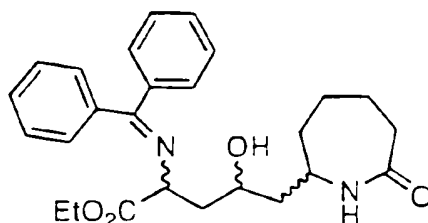
15 hexahydro-7-[(oxiran-2-yl)methyl]-1H-azepin-2-one



The title product isomer B of EXAMPLE 104 (2.99 g, 19.5
20 mmol) in 150 mL of CH_2Cl_2 was refluxed with meta-
chloroperbenzoic acid (MCPBA, 5.05 g, 29.3 mmol) for 3 hr.
After stirring at room temperature overnight, an
additional 1.0 g (5.8 mmol) of MCPBA was added and the
reaction re-heated to reflux for an additional 6 hr.
25 Solvent removal, followed by dissolution in EtOAc (150 mL)
and washing 3 x 50 mL with saturated NaHCO_3 provided crude
desired product. Purification via flash column
chromatography using 100% EtOAc and deactivated silica gel

EXAMPLE 242

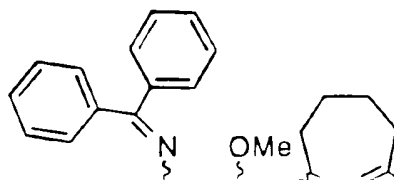
ethyl α -[(diphenylmethylene)amino]hexahydro-7-oxo-1H-
 5 azepine-2-pentanoate



Under an argon atmosphere, the anion of title product
 10 isomer B of EXAMPLE 241 (1.0 g, 5.91 mmol) is formed in
 tetrahydrofuran (THF, 30 mL) at -78°C with lithium
 bis(trimethylsilyl)amide in THF (5.91 mmol). The solution
 is warmed to -60°C , then cooled back to -78°C . To this
 is added the anion of N-(diphenylmethylene)glycine ethyl
 15 ester (formed by its reaction with lithium
 bis(trimethylsilyl)amide in THF (5.91 mmol) at -78°C .
 The solution is allowed to warm to room temperature
 overnight. Quenching with saturated NH_4Cl , followed by
 extraction into EtOAc (3 x 100 mL) provides crude title
 20 material and its lactone derivative. Purification via
 flash column chromatography yields clean title compound.

EXAMPLE 243

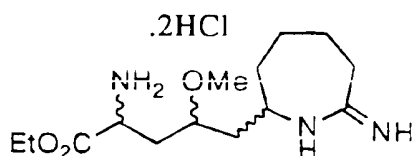
25 ethyl α -[(diphenylmethylene)amino]-3,4,5,6-tetrahydro- γ -
 dimethoxy-2H-azepine-2-pentanoate



The title product of EXAMPLE 242 is treated with trimethyloxonium tetrafluoroborate (two equivalents) in CH_2Cl_2 by the method of EXAMPLE 26 to yield title material.

EXAMPLE 244

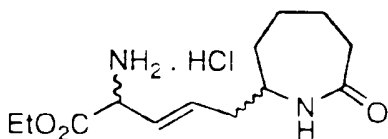
ethyl α -amino-7-imino- γ -methoxy-1H-azepine-2-pentanoate, dihydrochloride



The product of EXAMPLE 243 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27. This material is then lyophilized from aqueous HCl to generate the title material.

EXAMPLE 245

ethyl 2-amino-5-(hexahydro-7-oxo-1H-azepin-2-yl)-3-pentenoate, monohydrochloride



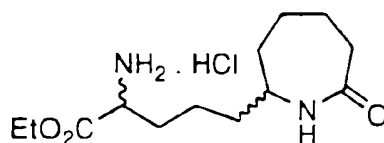
The product of EXAMPLE 242 is stirred with aqueous HCl to yield the title product.

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EXAMPLE 246

ethyl α -aminohexahydro-7-oxo-1H-azepine-2-pentanoate,
monohydrochloride

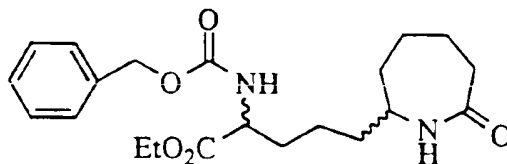
5



The product of EXAMPLE 245 is reduced via hydrogenation
using palladium on carbon as catalyst to produce the title
10 material.

EXAMPLE 247

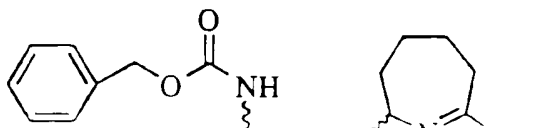
ethyl hexahydro-7-oxo- α [[(phenylmethoxy) carbonyl] amino] -
15 1H-azepine-2-pentanoate



The product of EXAMPLE 246 is treated with benzyl
20 chloroformate under standard conditions to yield title
product.

EXAMPLE 248

25 ethyl 3,4,5,6-tetrahydro-7-methoxy- α
[[(phenylmethoxy) carbonyl] amino] -2H-azepine-2-pentanoate



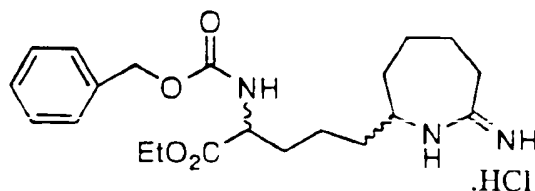
The product of EXAMPLE 247 is treated with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the method of EXAMPLE 26 to yield title material.

5

EXAMPLE 249

ethyl hexahydro-7-imino- α [[(phenylmethoxy) carbonyl] amino]-1H-azepine-2-pentanoate, monohydrochloride

10



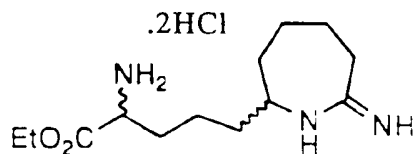
The product of EXAMPLE 248 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

15

EXAMPLE 250

ethyl α -aminohexahydro-7-imino-1H-azepine-2-pentanoate, dihydrochloride

20



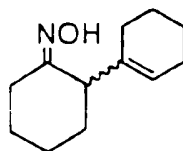
The product of EXAMPLE 249 is reduced using hydrogen and Pd/C as catalyst to yield the title product after lyophilization from aqueous HCl.

25

149

EXAMPLE 251

2-(cyclohexen-1-yl)cyclohexanone, oxime



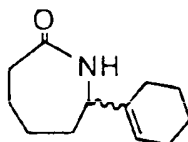
5

A sample of the 2-(1-cyclohexenyl)cyclohexanone (Lancaster) is converted to the title compound by the method of EXAMPLE 24 using hydroxylamine hydrochloride and NaOAc in a mixture of EtOH and water.

EXAMPLE 252

7-(cyclohexen-1-yl)hexahydro-1H-azepin-2-one

15



The product of EXAMPLE 251 is converted to the title compound by stirring it with the reagent trimethylsilyl polyphosphate in benzene (preformed by refluxing a mixture of phosphorous pentoxide and hexamethyldisiloxane in benzene until the mixture becomes homogeneous in appearance) at room temperature overnight followed by an aqueous quench and workup.

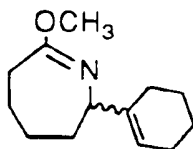
25

150

EXAMPLE 253

2-(cyclohexen-1-yl)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine

5

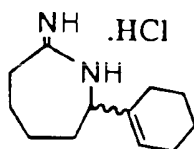


The product of EXAMPLE 252 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

EXAMPLE 254

7-(cyclohexen-1-yl)hexahydro-1H-azepin-2-imine, monohydrochloride

15

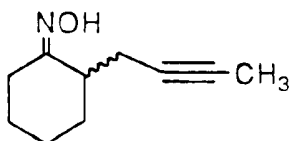


The product of EXAMPLE 253 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27 to generate the title material.

EXAMPLE 255

2-(2-butynyl)cyclohexanone, oxime

25



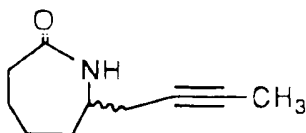
151

A sample of the 2-carboethoxycyclohexanone is reacted with 1-bromo-2-butyne by the method of EXAMPLE 202 using potassium carbonate in DMF at 60 °C followed decarboethoxylation in refluxing mixture of DMSO, lithium chloride, and water followed by conversion to its oxime using a mixture of hydroxylamine hydrochloride, NaOAc, EtOH and water.

EXAMPLE 256

10

7-(2-butyne)hexahydro-1H-azepin-2-one

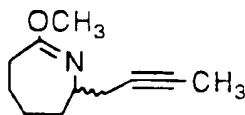


15 The product of EXAMPLE 255 is converted to the title compound by the method of EXAMPLE 29 using benzene sulfonylchloride.

EXAMPLE 257

20

2-(2-butyne)-3,4,5,6-tetrahydro-7-methoxy-2H-azepine



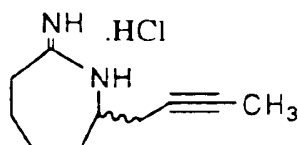
25 The product of EXAMPLE 256 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

152

EXAMPLE 258

7-(2-butynyl)hexahydro-1H-azepin-2-imine,
monohydrochloride

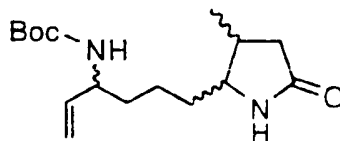
5



The product of EXAMPLE 257 in MeOH is reacted with
ammonium chloride by the method of EXAMPLE 27 to generate
10 the title material.

EXAMPLE 259

1,1-dimethylethyl N-[1-ethenyl-4-(3-methyl-5-
15 oxopyrrolidin-2-yl)butyl]carbamate



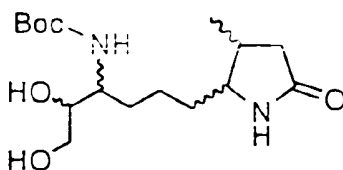
To a stirring solution of the product of EXAMPLE 238 (20
20 mmol) in dry toluene cooled to -70°C is added dropwise 1M
DIBAL-H in toluene (40 mL, 40 mmol). The solution is
stirred for an additional 20 min, and the reaction is
quenched with MeOH. Upon removal of the ice bath, 150 mL
of saturated solution of Rochelle salt is added to the
25 reaction. After stirring for 1 h, the layers are
separated. The aqueous layer is extracted with EtOAc.
The combined organic layers are washed with H₂O, dried,
filtered, and concentrated. The residue is purified by
chromatography to yield the aldehyde which is directly
30 used in the next step. To a stirring suspension of

153

hexamethyldisilazide in toluene (12.2 mL, 6.1 mmol). After stirring for 1.5 h, the aldehyde from above (6.1 mmol) in Et₂O is added. After 16 h, a white solid is filtered from the reaction and the filtrate is concentrated. The residue is purified by chromatography to yield the title compound.

EXAMPLE 260

10 1,1-dimethylethyl N-[1-(1,2-dihydroxyethyl)-4-(3-methyl-5-oxopyrrolidin-2-yl)butyl]carbamate



15 To a stirring solution of the compound from EXAMPLE 259 (3.3 mmol) in 80 mL of acetone:H₂O (3:1) is added N-methylmorpholine N-oxide (0.64 g, 4.8 mmol) and 2.5 % OsO₄ in t-BuOH (3.4 mL, 3.4 mmol). After 18 h, 120 mL of H₂O, 8 g of celite, and 1.6 g Na₂S₂O₄ is added to the reaction.

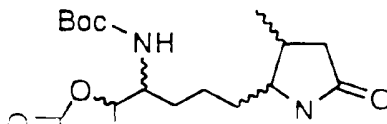
20 The reaction is filtered through a pad of wet celite. To the filtrate is added 200 mL of 1M KHSO₄. The filtrate is extracted with 3x 200 mL EtOAc. The combined organic layers are dried, filtered, and stripped. The residue is purified by chromatography to yield the title compound.

25

EXAMPLE 261

1,1-dimethylethyl N-[4-(3-methyl-2-oxopyrrolidin-2-yl)-1-(2-oxo-1,3-dioxolan-4-yl)butyl]carbamate

30

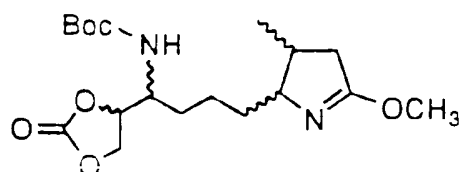


The product of EXAMPLE 260 in pyridine is treated with phosgene in toluene for 1 h, to produce the title material.

5

EXAMPLE 262

1,1-dimethylethyl N-[4-(3,4-dihydro-5-methoxy-3-methyl-2H-pyrrol-2-yl)-1-(2-oxo-1,3-dioxolan-4-yl)butyl]carbamate



10

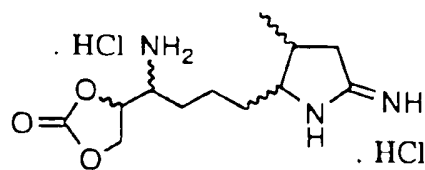
The product of EXAMPLE 261 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

15

EXAMPLE 263

4-[1-amino-4-(5-imino-3-methylpyrrolidin-2-yl)butyl]-1,3-dioxolan-2-one, dihydrochloride

20



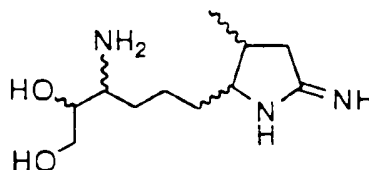
The product of EXAMPLE 262 in MeOH is reacted with ammonium chloride by the method of EXAMPLE 27, then treated with 3M HCl/EtOAc to generate the title material.

25

155

EXAMPLE 264

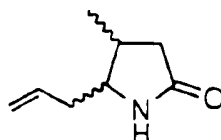
3-amino-6-(5-iminopyrrolidin-2-yl)-1,2-hexanediol



The product of EXAMPLE 263 is treated with aqueous barium hydroxide at 70 °C to yield the title material.

EXAMPLE 265

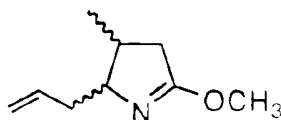
4-methyl-5-(2-propenyl)pyrrolidin-2-one



The product of EXAMPLE 235 is treated with PTSA in refluxing toluene, with a Dean-Stark trap to remove water. The solvent is removed to yield the title material.

EXAMPLE 266

3,4-dihydro-5-methoxy-3-methyl-2-(2-propenyl)-2H-pyrrole



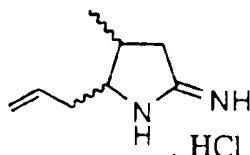
The product of EXAMPLE 265 is reacted with trimethyloxonium tetrafluoroborate by the method of EXAMPLE 26 to produce the title material.

156

EXAMPLE 267

4-methyl-5-(2-propenyl)pyrrolidin-2-imine,
monohydrochloride

5

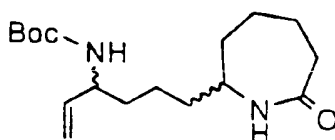


The product of EXAMPLE 266 in MeOH is reacted with
ammonium chloride by the method of EXAMPLE 27 to generate
the title material.

EXAMPLE 268

1,1-dimethylethyl N-[4-(hexahydro-7-oxo-1H-azepin-2-yl)-1-(2-propenyl)butyl]carbamate

15



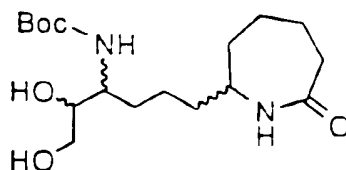
The product of EXAMPLE 246 is treated with di-t-
butyldicarbonate by the method of EXAMPLE 238. The
resulting Boc-protected product is then reacted with DIBAL
and then methyltriphenyl-phosphonium bromide by the method
of EXAMPLE 260 to generate the title material.

25

EXAMPLE 269

1,1-dimethylethyl N-[1-(1,2-dihydroxyethyl)-4-(hexahydro-7-oxo-1H-azepin-2-yl)butyl]carbamate

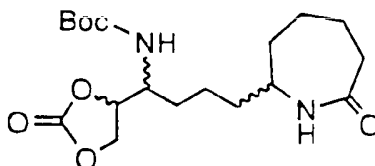
157



To the product of EXAMPLE 268 in a mixture of acetone and THF is added osmium tetroxide. An aqueous solution of morpholine N-oxide is then added to the reaction and the mixture is stirred at room temperature overnight. Sodium bisulfite is then added and this mixture after diluting with EtOAc is washed with brine, dried, filtered and stripped of all solvent under reduced pressure. The residue is purified by chromatography to yield the title compound.

EXAMPLE 270

1,1-dimethylethyl N-[4-(hexahydro-7-oxo-1H-azepin-2-yl)-1-(2-oxo-1,3-dioxolan-4-yl)butyl]carbamate

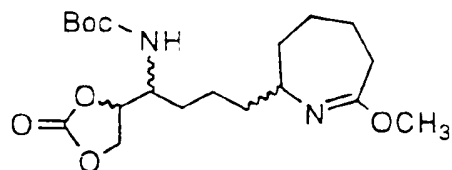


The product of EXAMPLE 269 is reacted with phosgene by the method of EXAMPLE 261, to generate the title material.

EXAMPLE 271

1,1-dimethylethyl N-[1-(2-oxo-1,3-dioxolan-4-yl)-4-(3,4,5,6-tetrahydro-7-methoxy-2H-azepin-2-yl)butyl]carbamate

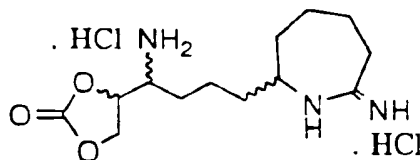
158



The product of EXAMPLE 270 is reacted with
 trimethyloxonium tetrafluoroborate by the method of
 5 EXAMPLE 26 to produce the title material.

EXAMPLE 272

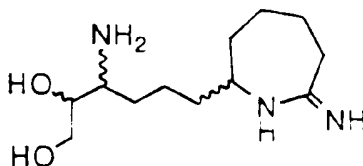
4-[1-amino-4-(hexahydro-7-imino-1H-azepin-2-yl)butyl]-1,3-
 10 dioxolan-2-one, dihydrochloride



The product of EXAMPLE 271 in MeOH is reacted with
 15 ammonium chloride by the method of EXAMPLE 27. This
 product is then treated with 3M HCl/EtOAc to generate the
 title material.

EXAMPLE 273

20 3-amino-6-(hexahydro-7-imino-1H-azepin-2-yl)-1,2-
 hexanediol



25

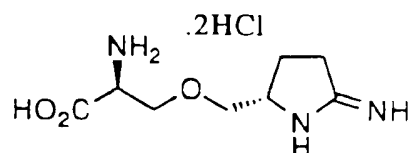
The product of EXAMPLE 272 is treated with aqueous barium

159

EXAMPLE 274

2S-amino-3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]propanoic
acid, dihydrochloride

5

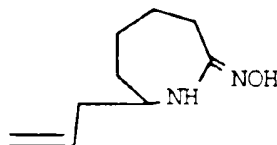


The product of EXAMPLE 229 in 2N HCl is refluxed for 1 h,
followed by lyophilization to generate the title material.

10

EXAMPLE 275

hexahydro-7-(2-propenyl)-1H-azepin-2-one, oxime



15

Into a 50 mL roundbottom flask under an argon atmosphere
was placed hydroxylamine hydrochloride (0.14g, 2.02 mmol)
and sodium methoxide (0.107 g, 1.99 mmol) in methanol (15
20 mL). To this was added the product of EXAMPLE 106 (0.29
g, 1.73 mmol). The reaction was heated to reflux for 12.5
h. The reaction was cooled to room temperature and all
solvent removed in vacuo. The product was purified via
reverse phase chromatography using a YMC ODS2 (20 x 25 mm)
25 column and a mobile phase of 30 % acetonitrile/water.

¹H NMR (400 MHz, D₂O) δ 5.9-5.8 (m, 1H), 5.3-5.15 (m, 2H),
3.8-3.7 (m, 1H), 2.75-2.65 (m, 1H), 2.6-2.4 (m, 3H), 2.0-
1.85 (m, 3H), 1.75-1.6 (m, 1H), 1.55-1.4 (m, 2H).

30

Elemental analysis: C₁₀H₁₆N₂O · 1.3 HCl · 1.1 H₂O

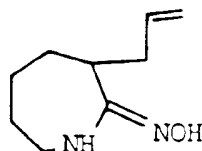
160

	C	H	N	Cl
Calculated:	45.91	8.35	11.90	19.57
Found:	45.96	8.17	11.65	19.67

5

EXAMPLE 276

hexahydro-2-(2-propenyl)-1H-azepin-2-one, oxime



10

Following the method of EXAMPLE 275, the title compound was prepared from the title product of EXAMPLE 105.

1H NMR (300 MHz, D2O) δ 5.9-5.7 (m, 1H), 5.3-5.1 (m, 2H), 3.6-3.5 (m, 2H), 2.85-2.75 (m, 1H), 2.65-2.55 (m, 1H), 2.45-2.35 (m, 1H), 1.9-1.5 (m, 7H).

15

Elemental analysis: C₉H₁₆N₂O · 1.05 HCl · 0.5 H₂O (MW = 217.33)

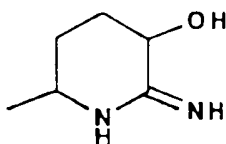
20

	C	H	N	Cl
Calculated:	49.74	8.46	12.89	17.13
Found:	49.73	8.11	12.82	17.30

25

EXAMPLE 277

3-hydroxy-2-imino-6-methylpiperidine acetate



•HOAc

30

The method of preparation of 2-imino-4-methylpiperidine

161

was run at 55°C. Product was obtained as a dark solid which was recrystallized from EtOH/EtOAc to give light amber crystals. The analysis of the product was found to be consistent with the proposed structure. m.p. 158-
5 160°C. $MH^+ = 129$; 1H NMR (D_2O) : δ 4.40 - 4.30 (m, 1H); 3.60 - 3.40 (m, 1H); 2.00 - 1.40 (m, 4H); 1.72 (s, 3H); 1.10 (d, $J = 7$ Hz, 3H).

Elemental analysis: $C_8H_{16}N_2O_3 \cdot (0.15 H_2O)$

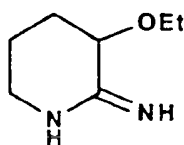
10

	C	H	N
Calculated:	50.33	8.61	14.67
Found:	50.33	8.54	14.66

15

EXAMPLE 278

3-ethoxy-2-imino-6-methylpiperidine hydrochloride



•HCl

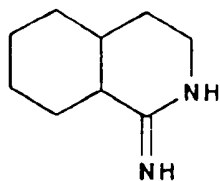
20

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 3-ethoxy-2-nitropyridine to the title compound except the reaction was run at 55°C. Product was obtained as a dark oil which was purified by
25 C-18-reverse phase chromatography, eluting with H_2O/CH_3CN . Fractions containing the product were lyophilized, redissolved in 1N HCl and lyophilized to give the product as a light yellow oil. The analysis of the product was found to be consistent with the proposed structure. $MH^+ =$
30 143; 1H NMR (D_2O) : δ 4.35 - 4.20 (m, 1H); 3.8 - 3.5 (m, 2H); 3.30 - 3.10 (m, 2H); 2.25 - 2.10 (m, 1H); 2.0 - 1.5 (m, 3H); 1.07 (t, $J = 7$ Hz, 3H).

162

EXAMPLE 279

2-imino-decahydroisoquinoline acetate



•HOAc

5

2-amino-isoquinoline (1 g), palladium black (0.5 g) and ammonium formate (1 g) were suspended in methanol (150 ml) with stirring. The reaction mixture was stirred over the weekend at 40°C and the catalyst was removed by filtration. The filtrate was taken down to dryness and the residue was triturated with dried ether to give 3,4-benzo-2-iminopiperidine formate as a solid. ES-MS : MH⁺ = 147.

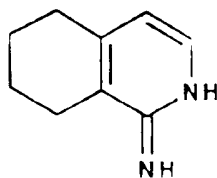
15

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 3,4-benzo-2-iminopiperidine to the title compound except platinum oxide was used as the catalyst. The product was recrystallized from EtOAc/EtOH to give a light tan solid. The analysis of the product was found to be consistent with the proposed structure. MH⁺ = 153; ¹H NMR (D₂O) : δ 3.4 - 3.1 (m, 3H); 2.6 - 2.4 (m, 1H); 2.20 - 1.00 (m, 10H); 1.75 (s, 3H).

25

EXAMPLE 280

2-amino-5, 6, 7, 8-tetrahydroisoquinoline acetate



•HOAc

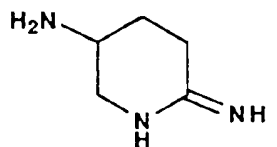
The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-aminoisoquinoline to the title compound except platinum oxide was used as the catalyst. The product was triturated with EtOH to give a white solid. The analysis of the product was found to be consistent with the proposed structure. ¹H NMR (D₂O) : δ 7.35 (d, J = 6 Hz, 1H); 6.55 (d, J = 6 Hz, 1H); 2.6 - 2.5 (m, 2H); 2.20 - 2.10 (m, 2H); 1.75 (s, 3H); 1.70 - 1.50 (m, 4H).

Elemental analysis: C₁₁H₁₆N₂O₂

	C	H	N
15 Calculated:	63.44	7.74	13.45
Found:	63.22	7.89	13.47

EXAMPLE 281

20 5-amino-2-iminopiperidine hydrochloride



•HCl

2,5-diaminopyridine dihydrochloride (1.2 g) and platinum oxide (500 mg) in ethanol (20 mL) and conc HCl (2 mL) were shaken on a Parr hydrogenation apparatus at 55 psi of hydrogen overnight. Product was obtained as a dark solid which was purified by C-18-reverse phase chromatography, eluting with H₂O/CH₃CN. Fractions containing the product were lyophilized, redissolved in 1N HCl and lyophilized to give the product as a yellow solid. The analysis of the product was found to be consistent with the proposed

164

2H); 3.4 - 3.25 (m, 1H); 2.75 - 2.65 (m, 2H); 2.25 - 2.15 (m, 1H); 2.15 - 1.85 (m, 1H).

Elemental analysis: $C_5H_{13}Cl_2N_3$

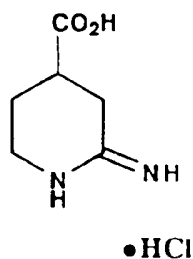
5

	C	H	N
Calculated:	32.27	7.04	22.58
Found:	32.43	7.00	22.48

10

EXAMPLE 282

2-imino-4-piperidine carboxylic acid hydrochloride



15

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-aminopyridine-4-carboxylic acid to the title compound except platinum oxide was used as the catalyst. Product dissolved in 3N HCl and lyophilized to give white solid, which was recrystallized from EtOH to give product as a white solid. The analysis of the product was found to be consistent with the proposed structure. m.p. 230-234°C. 1H NMR (D_2O) : δ 3.40 - 3.20 (m, 2H); 3.0 - 2.8 (m, 2H); 2.80 - 2.70 (m, 2H); 2.20 - 2.00 (m, 1H); 2.00 - 1.80 (m, 1H).

25

Elemental analysis: $C_6H_{11}ClN_2O_2$

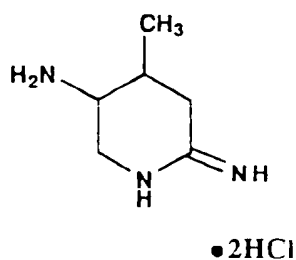
30

	C	H	N
Calculated:	40.35	6.21	15.68

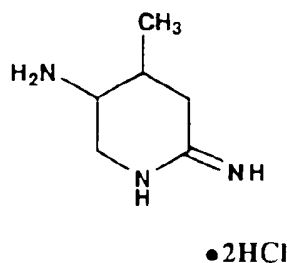
EXAMPLE 283

5-amino-2-imino-4-methylpiperidine dihydrochloride (cis and trans isomers)

5



(A)



(B)

The method of preparation of 5-amino-2-iminopiperidine hydrochloride was used to convert 2-amino-4-methyl-5-nitropyridine to the title compound. Product was obtained as a white solid, shown to be two isomers by ^1H NMR analysis. Recrystallization from EtOH/H₂O gave a white solid, shown to be one isomer (A) by ^1H NMR and tentatively assigned the trans configuration. The mother liquor was concentrated in vacuo and redissolved in warm EtOH. Upon cooling, the first crop was obtained which contains more (A). The second crop contains a mixture of (A) and (B). The third crop is pure (B), which was tentatively assigned the cis configuration. The analysis of the product was found to be consistent with the proposed structure. ^1H NMR (D₂O) of (A): δ 8.8 - 3.7 (m, 1H); 3.68 - 3.58 (m, 1H); 3.50 - 3.40 (m, 1H); 2.90 - 2.75 (m, 1H); 2.45 - 2.35 (m, 2H); 1.00 (d, J = 7 Hz, 3H). ^1H NMR (D₂O) of (B): δ 8.75 - 3.65 (m, 1H); 3.45 - 3.25 (m, 2H); 2.85 - 2.70 (m, 1H); 2.50 - 2.35 (m, 1H); 2.20 - 2.15 (m, 1H); 1.05 (d, J = 7 Hz, 3H).

Elemental analysis of (A): C₆H₁₅Cl₂N₃·(H₂O)

166

	C	H	N
Calculated:	33.04	7.86	19.26
Found:	33.01	7.39	19.20

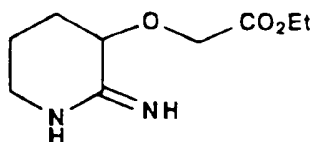
5 Elemental analysis of (B): $C_6H_{15}Cl_2N_3 \cdot (0.4 H_2O)$

	C	H	N
Calculated:	34.76	7.68	20.27
Found:	34.53	7.54	20.67

10

EXAMPLE 284

Ethyl (2'-imino)-2-(3'-piperidineoxy)acetate hydrochloride



15

•HCl

3-hydroxy-2-nitropyridine (5 g) and anhydrous potassium carbonate (5 g) were mixed in anhydrous DMF (75 mL) for 15 minutes. Ethyl bromoacetate was added and contents were stirred overnight. The contents were poured into ice water and extracted with EtOAc (2 x 200 mL). The EtOAc extracts were combined, dried (MgSO₄) and concentrated in vacuo to give 2'-nitro-2-(3'-pyridineoxy)acetate as a light yellow solid (6.6 g).

25

The method of preparation of 5-amino-2-iminopiperidine hydrochloride was used to convert 2'-nitro-2-(3'-pyridineoxy)acetate to the title compound. Purification by C-18-reverse phase chromatography and recrystallization from EtOH/EtOAc gave the product as a white solid.

30

The analysis of the product was found to be consistent

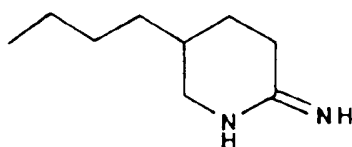
167

Elemental analysis: $C_9H_{17}ClN_2O_3 \cdot (0.25 H_2O)$

	C	H	N
Calculated:	44.82	7.31	11.61
5 Found:	44.92	7.62	11.75

EXAMPLE 285

2-imino-5-(n-butyl)piperidine acetate



•HOAc

10

Fusaric acid (2 g), diphenylphosphoryl azide (2.4 mL) and triethylamine (1.6 mL) in t-butanol (70 mL) were refluxed overnight. The contents were concentrated in vacuo and
15 treated with 25% aqueous HBr (20 mL) for 24 hours. After neutralizing with 50% NaOH, contents were extracted with CH_2Cl_2 , dried ($MgSO_4$) and concentrated in vacuo to give 2-amino-5-(n-butyl)pyridine as an oil (1.1 g).

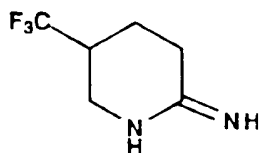
20 The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-5-(n-butyl)pyridine to the title compound except platinum oxide was used as the catalyst. Product was triturated with ether to give a white solid. The analysis of the product was found to be
25 consistent with the proposed structure. $MH^+ = 155$; 1H NMR (D_2O) : δ 3.35 - 3.25 (m, 1H); 2.85 - 2.75 (m, 1H); 2.60 - 2.35 (m, 2H); 1.85 - 1.55 (m, 2H); 1.75 (s, 3H); 1.35 - 1.05 (m, 7H); 0.75 - 0.65 (m, 3H).

30

168

EXAMPLE 286

2-imino-5-(trifluoromethyl)piperidine hydrochloride



•HCl

5

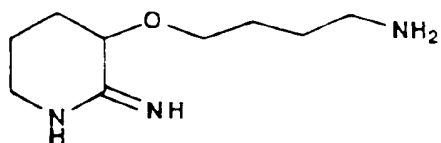
The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-3-chloro-5-(trifluoromethyl)pyridine to the title compound except platinum oxide was used as the catalyst. Product was triterated with ether to give a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 167$; 1H NMR (D_2O) : δ 6.65 - 3.50 (m, 1H); 3.40 - 3.20 (m, 1H); 2.85 - 2.45 (m, 3H); 2.15 - 2.00 (m, 1H); 1.80 - 1.60 (m, 1H).

Elemental analysis: $C_6H_{10}ClF_3N_2 \cdot (0.1 H_2O)$

	C	H	N
20 Calculated:	35.26	5.03	13.70
Found:	34.91	4.97	13.64

EXAMPLE 287

O-[3-(2-iminopiperidinyl)]-4-amino-1-butanol



•2HCl

minutes. 4-Bromo-butyronitrile (3.6 mL) was added and contents were stirred overnight. Contents were poured into ice water and 4-[2'-nitro-(3'-pyridineoxy)] butyronitrile, as a white solid, was filtered.

5

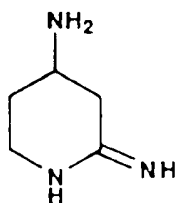
The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 4-[2'-nitro-(3'-pyridineoxy)]butyronitrile to the title compound except platinum oxide was used as the catalyst. Purification by
10 C-18 reverse phase chromatography and crystallization from EtOAc/EtOH gave the product as a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 185$; 1H NMR (D_2O) : δ 7.5 - 3.65 (m, 1H); 3.50 - 3.40 (m, 2H); 3.30 - 2.85 (m,
15 6H); 1.80 - 1.45 (m, 8H).

Elemental analysis: $C_9H_{21}Cl_2N_3O$

	C	H	N
20 Calculated:	41.87	8.20	16.28
Found:	41.83	8.33	15.98

EXAMPLE 288

25 4-amino-2-iminopiperidine dihydrobromide



•2HBr

4-Amino-3,5,6-trichloropicolinic acid (1.0 g),
30 diphenylphosphoryl azide (1.0 mL) and triethylamine (0.6 mL) in t-butanol (35 mL) were refluxed overnight.

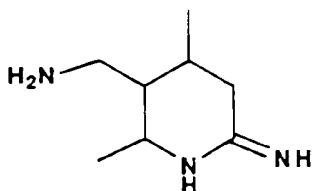
170

hours. 2,4-diamino-3,5,6-trichloropyridine dihydrobromide was filtered as a light yellow solid (1.2 g).

2,4-Diamino-3,5,6-trichloropyridine dihydrobromide (1.1 g) and platinum oxide (520 mg) in ethanol (50 mL) were shaken on a Parr hydrogenation apparatus at 55 psi of hydrogen for 48 hours. The contents were filtered and the filtrate was concentrated in vacuo leaving a waxy solid. The solid was triturated with ether/EtOH to give 4-amino-2-iminopiperidine dihydrobromide as a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 114$; 1H NMR (D_2O) : δ .80 3.60 (m, 1H); 3.55 - 3.25 (m, 1H); 3.08 - 2.95 (m, 1H); 2.76 - 2.62 (m, 1H); 2.25 - 2.13 (m, 1H); 1.95 - 1.80 (m, 1H).

EXAMPLE 289

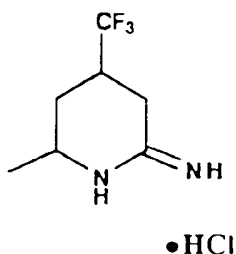
5-aminomethyl-2-imino-4,6-dimethylpiperidine dihydrochloride

**•2HCl**

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-5-cyano-4,6-dimethylpyridine to the title compound except platinum oxide was used as the catalyst. Product was treated with EtOH to give a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 156$; 1H NMR (D_2O) : δ .63 - 3.40 (m, 2H); 3.20 - 3.05 (m, 1H); 2.70 - 2.58 (m, 1H); 2.40 - 2.20 (m, 1H);

EXAMPLE 290

2-imino-6-methyl-4-(trifluoromethyl)piperidine
5 hydrochloride



10 2-chloro-6-methyl-4-(trifluoromethyl)pyridine (5.0 g) and
conc ammonium hydroxide (150 mL) were heated at 180°C in a
steel reaction vessel with mechanical stirring overnight.
The contents were allowed to cool and partitioned between
CH₂Cl₂ and water. The CH₂Cl₂ layer was dried (MgSO₄) and
15 concentrated in vacuo leaving 2-amino-6-methyl-4-
(trifluoromethyl)pyridine as a white solid.

The method of preparation of 2-imino-4-methylpiperidine
acetate was used to convert 2-amino-6-methyl-4-
20 (trifluoromethyl)pyridine to the title compound. Product
was triturated with EtOAc/EtOH to give a white solid. The
analysis of the product was found to be consistent with
the proposed structure. MH⁺ = 181; ¹H NMR (D₂O) : δ.60
- 3.40 (m, 1H); 2.80 - 2.50 (m, 3H); 2.20 - 2.05 (m,
25 1H); 1.42 - 1.25 (m, 1H); 1.15 (d, J = 7 Hz, 3H).

Elemental analysis: C₇H₁₂ClF₃N₂·(0.25 H₂O)

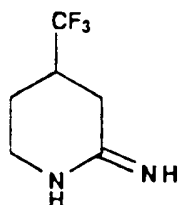
172

	C	H	N
Calculated:	38.02	5.70	12.67
Found:	37.98	5.54	12.84

5

EXAMPLE 291

2-imino-4-(trifluoromethyl)piperidine hydrochloride



•HCl

10

The method of preparation of 2-amino-6-methyl-4-(trifluoromethyl)pyridine was used to convert 2-chloro-4-(trifluoromethyl)pyridine to 2-amino-4-(trifluoromethyl)pyridine.

15

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-4-(trifluoromethyl)pyridine to the title compound. The product was triturated with EtOAc to give a white solid.

20

The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 167$; 1H NMR (D_2O): δ 3.45 - 3.35 (m, 1H); 3.30 - 3.20 (m, 1H); 2.85 - 2.55 (m, 3H); 2.10 - 2.00 (m, 1H); 1.80 - 1.60 (m, 1H).

25

Elemental analysis: $C_6H_{10}ClF_3N_2$

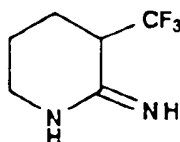
	C	H	N
Calculated:	35.57	4.98	13.83
Found:	35.17	4.76	13.70

30

173

EXAMPLE 292

2-imino-3-(trifluoromethyl)piperidine trifluoroacetate

•CF₃CO₂H

5

The method of preparation of 2-amino-6-methyl-4-(trifluoromethyl) pyridine was used to convert 2-chloro-3-(trifluoromethyl)pyridine to 2-amino-3-(trifluoromethyl)pyridine.

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-3-(trifluoromethyl)pyridine to the title compound. Product was crystallized from EtOAc/hexanes to give a white solid. The analysis of the product was found to be consistent with the proposed structure. MH⁺ = 167; ¹H NMR (D₂O) : δ 7.0 - 3.50 (m, 1H); 3.35 - 3.20 (m, 2H); 2.10 - 1.60 (m, 4H).

Elemental analysis: C₈H₁₀F₆N₂O₂

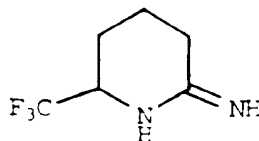
	C	H	N
Calculated:	34.30	3.60	10.00
Found:	34.55	3.65	10.01

25

174

EXAMPLE 293

2-imino-6-(trifluoromethyl)piperidine acetate



5

The method of preparation of 2-amino-6-methyl-4-(trifluoromethyl) pyridine was used to convert 2-chloro-6-(trifluoromethyl)pyridine to 2-amino-6-(trifluoromethyl) pyridine.

10

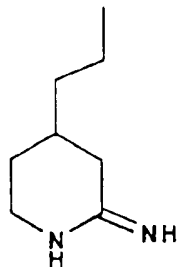
The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-6-(trifluoromethyl) pyridine to the title compound. Product was crystallized from EtOAc to give a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 167$; 1H NMR (D_2O) : δ 4.20 - 4.00 (m, 1H); 2.60 - 2.50 (m, 2H); 2.05 - 1.50 (m, 4H); 1.80 (s, 3H).

15

20

EXAMPLE 294

2-imino-4-(n-propyl)piperidine acetate



25

•HOAc

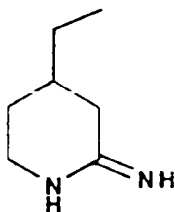
The method of preparation of 2-imino-4-methylpiperidine

175

the catalyst. Product was triturated with EtOAc to give a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 141$; 1H NMR (D_2O) : δ 3.35 - 3.05 (m, 2H); 2.60 - 2.40 (m, 1H); 2.15 - 2.00 (m, 1H); 1.80 - 1.60 (m, 2H); 1.78 (s, 3H); 1.35 - 1.05 (m, 5H); 0.75 - 0.65 (m, 3H).

EXAMPLE 295

10 2-imino-4-(n-ethyl)piperidine acetate



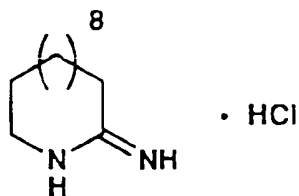
•HOAc

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-4-(n-ethyl)pyridine to the title compound except platinum oxide was used as the catalyst. The product was crystallized from cold EtOAc to give a white solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 127$; 1H NMR (D_2O) : δ 3.40 - 3.25 (m, 1H); 3.22 - 3.10 (m, 1H); 2.60 - 2.50 (m, 1H); 2.15 - 2.00 (m, 1H); 1.85 - 1.75 (m, 1H); 1.78 (s, 3H); 1.70 - 1.60 (m, 1H); 1.35 - 1.15 (m, 3H); 0.75 (t, $J = 7$ Hz, 3H)

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EXAMPLE 296

2-Iminododecamethylenimine Hydrochloride salt



5

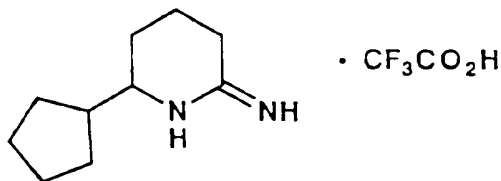
To a solution of 1g (0.0067mol) of trimethyloxonium tetrafluoroborate in 10mL of anhydrous chloroform was added 1.33g (0.0067mol) of 2-azacyclotridecanone. This mixture was stirred at reflux for four hours, then for 18 hours at 25°C. This mixture was then diluted with ethyl acetate, washed with dilute potassium carbonate, dried (MgSO₄), filtered and concentrated to afford 1.3g of a pink oil. This oil was dissolved in 25mL of methanol and 0.33g (0.006mol) of ammonium chloride was added. After stirring at 25°C for 72 hours, the mixture was concentrated to afford 0.6g of a white solid. It was extracted with water, filtered and the filter was lyophilized to afford 2-iminododecamethylenimine hydrochloride salt as a white fluffy solid.

¹H-NMR(D₂O) 1.1-1.3 (m, 14H), 1.45-1.65 (m, 4H), 2.35 (m, 2H), 3.2 (m, 2H); Mass Spectra, M+H=197; Elemental analysis Calcd. for C₁₂H₂₅N₂Cl₁ + 2/3 N₁H₄Cl₁: C, 53.65; H, 10.39; N, 13.92. Found C, 53.42, H, 10.32, N, 13.58.

25

EXAMPLE 297

2-Imino-6-Cyclopentylpiperidine Trifluoroacetic acid salt



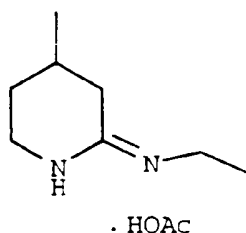
177

To a solution of 1g (0.0067mol) of trimethyloxonium tetrafluoroborate in 20mL of anhydrous chloroform was added 0.5g (0.003mol) of 6-cyclopentylvalerolactam. This mixture was stirred at reflux for three hours. This mixture was allowed to cool to 25°C, washed with dilute sodium bicarbonate, dried (MgSO₄), filtered and concentrated to afford a yellow oil. This oil was dissolved in 25mL of methanol and 0.16g of ammonium chloride was added. After stirring at 25°C for 18 hours, the mixture was concentrated to afford a white semisolid. Chromatography (C-18) afforded the pure 2-imino-6-cyclopentylpiperidine trifluoroacetic acid salt as a white solid. ¹H-NMR(D₂O) 1.05-1.2 (m, 2H), 1.35-1.95 (m, 11H), 2.3-2.55 (m, 2H), 3.15-3.25 (m, 1H); Mass Spectra, M+H=167.

EXAMPLE 298

(2-Ethylimino)-4-methylpiperidine acetate

20



Hydrobromic acid (48%, 39.5 mL) was cooled to 0°C and 2-amino-4-picoline (Aldrich, 8.6 g, 0.08 mole) was added in portions. At 0°C, bromine (12 mL, 0.234 mole) was added slowly dropwise, followed by dropwise addition of a solution of sodium nitrite (14.0 g) in water (20 mL) at 0°C. The contents were stirred 1-1/2 hours at 0°C before adding 50% aqueous sodium hydroxide (60 g), keeping the temperature less than 20°C during the addition. Contents were stirred 1 hour and extracted with ether (2 x 200 mL).

178

vacuo leaving an orange oil (12.4 g). The oil was distilled on a kugelrohr apparatus at 40°C (0.25 mm) to give 2-bromo-4-methylpyridine as a yellow oil (10.3 g).

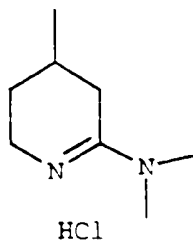
- 5 2-Bromo-4-methylpyridine (1.5 g, 0.02 mole) and aqueous ethylamine (70%, 100 mL) were heated at 150°C overnight in a steel pressure reactor. Contents were allowed to cool and concentrated in vacuo. The residue was triturated with CH₂Cl₂ and a white solid was filtered and discarded.
- 10 The filtrate was concentrated in vacuo leaving an oil (950 mg). The oil was distilled on a kugelrohr apparatus at 90°C (0.35 mm) to give 2-(ethylamino)-4-methylpyridine as a white solid (670 mg).
- 15 The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-(ethylamino)-4-methylpyridine to the title compound except platinum oxide was used as the catalyst. The analysis of the product, obtained as an oil, was found to be consistent with the
- 20 proposed structure. MH⁺ = 141; ¹H NMR (D₂O): 3.40 - 3.10 (m, 2H); 3.00 (q, J = 6 Hz, 2H); 2.50 - 2.40 (m, 1H); 2.10 - 1.90 (m, 1H); 1.83 (s, 3H); 1.80 - 1.65 (m, 4H); 1.40 - 1.20 (m, 1H); 1.02 (t, J = 6 Hz, 3H); 0.83 (d, J = 6 Hz, 3H).

25

EXAMPLE 299

2-(N,N-dimethylamino)-4-methyl-3,4,5,6-tetrahydropyridine hydrochloride

30

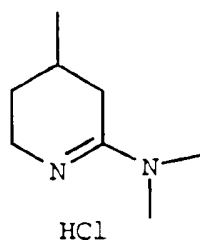


The method of preparation of 2-(ethylamino)-4-methylpyridine was used to convert 2-bromo-4-methylpyridine to 2-(N, N-dimethylamino)-4-methylpyridine.

- 5 The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-(N, N-dimethylamino)-4-methylpyridine to the title compound except platinum oxide was used as the catalyst. The product was obtained as a clear colorless oil which was dissolved in 3N HCl and
- 10 lyophilized to give the desired product as a waxy colorless solid. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 141$; 1H NMR (D_2O): 3.44 - 3.32 (m, 1H); 3.28 - 3.16 (m, 1H); 3.00 (s, 3H); 2.90 (s, 3H); 2.76 - 2.64 (m, 1H); 2.08 - 1.94 (m, 1H); 1.88 - 1.68 (m, 2H); 1.35 - 1.18 (m, 1H); 0.52 (d, $J = 6$ Hz, 3H).
- 15

EXAMPLE 300

- 20 2'-(2-aminoethylimino)-5'-(trifluoromethyl)piperidine dihydrochloride

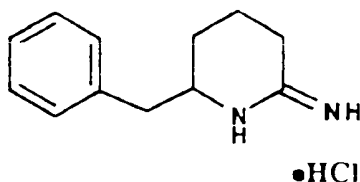


- 25 The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2'-(2-aminoethylamino)-3'-chloro-5'-(trifluoromethyl)pyridine to the title compound. The analysis of the product, obtained as an oil, was found to be consistent with the proposed structure. $MH^+ = 210$;
- 30 1H NMR (D_2O): 3.70 - 3.35 (m, 4H); 3.18 (t, $J = 6$ Hz, 2H); 2.95 - 2.60 (m, 3H); 2.20 - 2.00 (m, 1H); 1.90 - 1.70

180

EXAMPLE 301

6-Benzyl-2-iminopiperidine hydrochloride



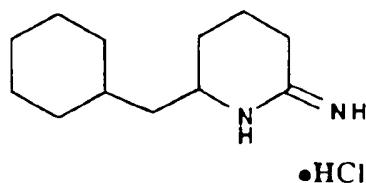
- 5 2-benzylpyridine (Aldrich, 2.5 g, 0.015 mole), sodium amide (780 mg, 0.02 mole) and N, N-dimethylaniline (25 mL) were refluxed overnight. The contents were allowed to cool and were partitioned between ether and water. The ether layer was dried (MgSO₄) and concentrated in vacuo leaving an oil. The oil was purified by chromatography. The purified material was dissolved in 1N HCl, lyophilized, and triturated with EtOAc to give 2-amino-6-benzylpyridine as a white solid.
- 15 The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-6-benzylpyridine to the title compound. The product was obtained as an oil which was purified by C-18 reverse phase chromatography to give a white solid. The solid was dissolved in 1 N HCl, lyophilized, and recrystallized from EtOH/EtOAc to give the desired product as a white solid. The analysis of the product was found to be consistent with the proposed structure. MH⁺ = 189; ¹H NMR (CDCl₃): 9.85 (s, 1H); 8.95 (s, 1H); 8.62 (s, 1H); 7.40 - 7.10 (m, 5H); 3.80 - 3.60 (m, 1H); 3.20 - 3.00 (m, 1H); 2.90 - 2.70 (m, 2H); 2.65 - 2.45 (m, 1H); 2.42 - 2.25 (m, 2H); 1.92 (m, 2H); 1.75 (m, 1H); 1.50 - 1.35 (m, 1H).
- 25

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EXAMPLE 302

2-(cyclohexylmethyl)-6-iminopiperidine hydrochloride

5

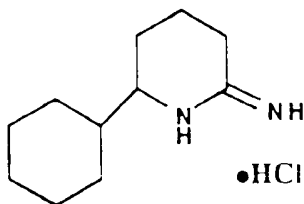


The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-6-benzylpyridine to the title compound except platinum oxide was used as the catalyst. The product was obtained as an oil which was dissolved in 1 N HCl and lyophilized to give a white solid. The solid was recrystallized from EtOAc to give the desired product as white crystals. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 195$; 1H NMR ($CDCl_3$): 9.60 (s, 1H); 8.90 (s, 1H); 8.70 (s, 1H); 3.60 - 3.40 (m, 1H); 2.90 - 2.70 (m, 1H); 2.70 - 2.50 (m, 1H); 2.10 - 1.80 (m, 2H); 1.80 - 1.00 (m, 13H); 1.00 - 0.80 (m, 2H).

20

EXAMPLE 303

2-cyclohexyl-6-iminopiperidine hydrochloride



25

The method of preparation of 2-amino-6-benzylpyridine was used to convert 2-phenylpyridine (Aldrich) to 2-amino-6-

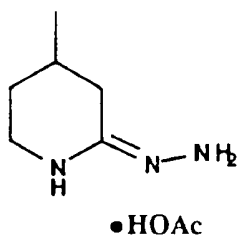
182

The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-amino-6-phenylpyridine to the title compound except the reaction was run at 55°C. The product was obtained as an oil which was crystallized from EtOH/EtOAc to give the desired product as a white solid.

MH⁺ = 181; ¹H NMR (CDCl₃): 3.30 - 3.15 (m, 1H); 2.50 - 2.30 (m, 2H); 1.85 - 1.68 (m, 2H); 1.65 - 1.20 (m, 8H); 1.20 - 0.80 (m, 5H).

EXAMPLE 304

4-Methylpiperidine-2-hydrazone acetate

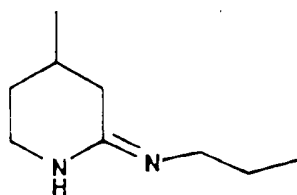


The method of preparation of 2-imino-4-methylpiperidine acetate was used to convert 2-hydrazinopyridine (Aldrich) to the title compound except the reaction was run in glacial acetic acid/water (2:1) for solubility and platinum oxide was used for the catalyst. The product was obtained as a clear colorless oil which crystallized under EtOAc and was recrystallized from ethanol to give the desired as white crystals. The analysis of the product was found to be consistent with the proposed structure. MH⁺ = 114; ¹H NMR (D₂O): 3.15 - 3.10 (m, 2H); 2.60 - 2.50 (m, 2H); 1.98 (s, 3H); 1.80 - 1.60 (m, 4H).

183

EXAMPLE 305

4-Methyl-2-(propylimino)piperidine hydrochloride



•HCl

5

The method of preparation of 2-(ethylimino)-4-methylpiperidine acetate was used to convert 4-methyl-2-(propylamino)pyridine hydrochloride to the title compound. The product was obtained as a clear colorless oil which crystallized under EtOAc. The analysis of the product was found to be consistent with the proposed structure. $MH^+ = 155$; 1H NMR (D_2O): 3.45 - 3.20 (m, 2H); 3.05 (t, $J = 6$ Hz, 2H); 2.60 - 2.45 (m, 1H); 2.20 - 2.00 (m, ; 1.95 - 1.70 (m, 2H); 1.60 - 1.40 (m, 2H); 1.40 - 1.25 (m, 1H); 0.90 (d, $J = 6$ Hz, 3H); 0.80 (t, $J = 6$ Hz, 3H).

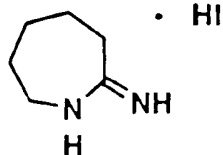
15

EXAMPLE 306

2-Iminohexamethylenimine Hydroiodide salt

J. Med. Chem. 21(10), 1044-54 (1978)

20



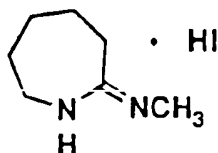
To a solution of 5g (0.039mol) of thiocaprolactam in 100mL of acetone was added 6.4g (0.045mol) of iodomethane. This mixture was stirred two days at 25°C. Filtration afforded 9.5g of the thio-iminoether hydroiodide salt as a white solid, mp 177-181°C. Three grams of this iminoether was dissolved in 80ml of ethanol saturated with anhydrous

25

three days. Concentration to a reduced volume followed by ether trituration afforded 2.2g of the title product as a white solid, mp 135-141°C. $^1\text{H-NMR}(\text{D}_2\text{O})$ 1.45-1.55 (m, 2H), 1.55-1.7 (m, 4H), 2.5 (m, 2H), 3.28 (m, 2H); Mass Spectra, $\text{M}+\text{H}=113$; Elemental analysis Calcd. for $\text{C}_6\text{H}_{13}\text{N}_2\text{I}$: C, 30.02; H, 5.46; N, 11.67. Found C, 29.99, H, 5.49, N, 11.61.

EXAMPLE 307

10 2-(Methylimino)hexamethylenimine Hydroiodide salt

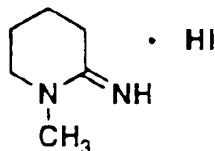


To a solution of 1g (0.0037mol) of the thio-iminoether from EXAMPLE 306 was added 40mL of ethanol saturated with anhydrous methylamine. This mixture was sealed and stirred at 25°C for three days. Concentration to a reduced volume followed by ether trituration afforded 0.9g of the title product as a white solid, mp 169-171°C. $^1\text{H-NMR}(\text{D}_2\text{O})$ 1.45-1.65 (m, 6H), 2.48 (m, 2H), 2.68 (s, 3H), 3.3 (m, 2H); Mass Spectra, $\text{M}+\text{H}=127$; Elemental analysis Calcd. for $\text{C}_7\text{H}_{15}\text{N}_2\text{I}$: C, 33.09; H, 5.95; N, 11.02. Found C, 33.31, H, 5.94, N, 10.97.

185

EXAMPLE 308

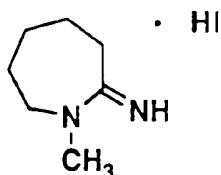
1-Methyl-2-iminopentamethylenimine Hydroiodide salt



To a solution of 2g (0.0155mol) of N-methylthiovalerolactam in 40mL of acetone was added 2.4g (0.017mol) of iodomethane. This mixture was stirred three days at 25°C. Filtration and trituration with ether afforded 4g of the thio-iminoether hydroiodide salt as a white solid, mp 153-155°C. One gram of this iminoether was dissolved in 50mL of ethanol saturated with anhydrous ammonia. This mixture was sealed and stirred at 25°C for eighteen hours. Concentration to a reduced volume followed by ether trituration afforded 0.8g of the title product as a white solid, mp 157-158°C. ¹H-NMR(D₂O) 1.6-1.7 (m, 2H), 1.7-1.8 (m, 2H), 2.5 (t, 2H), 2.95 (s, 3H), 3.38 (t, 2H); Mass Spectra, M+H=113; Elemental analysis Calcd. for C₆H₁₃N₂I₁: C, 30.02; H, 5.46; N, 11.67. Found C, 30.16, H, 5.49, N, 11.63.

EXAMPLE 309

1-Methyl-2-iminohexamethylenimine Hydroiodide salt



To a solution of 2g (0.014mol) of N-methylthiocaprolactam

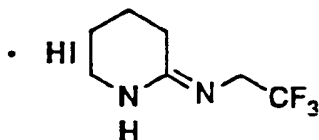
186

Filtration and trituration with ether afforded 3.8g of the thio-iminoether hydroiodide salt as a white solid, mp 138-142°C. One gram of this iminoether was dissolved in 50mL of ethanol saturated with anhydrous ammonia. This mixture
5 was sealed and stirred at 25°C for eighteen hours. Concentration to a reduced volume followed by ether trituration afforded 0.8g of the title product as a white solid, mp 137-139°C. ¹H-NMR(D₂O) 1.55-1.7 (m, 6H), 2.58 (m, 2H), 3.02 (s, 3H), 3.55 (m, 2H); Mass Spectra,
10 M+H=127; Elemental analysis Calcd. for C₇H₁₅N₂I: C, 33.09; H, 5.95; N, 11.02. Found C, 33.12, H, 6.01, N, 11.07.

EXAMPLE 310

15

2-(Trifluoroethylimino)pentamethylenimine Hydroiodide salt



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A mixture of 100g (0.23mol) of P₄S₁₀ and 24g (0.23mol) of Na₂CO₃ in 1.5L of anhydrous THF was stirred vigorously with a mechanical stirrer for thirty minutes. To this stirred mixture was added 19g (0.19mol) of valerolactam.
25 After stirring for three hours, the solution was diluted with 1L of 10% aqueous Na₃PO₄, 750mL of ethyl acetate and 750mL of hexanes. Organic layer was separated and the aqueous layer was extracted with 500mL of ethyl acetate. The organic extracts were combined, dried (MgSO₄),
30 filtered through silica gel and concentrated to afford a white semi-solid. Trituration with hexanes-ether afforded 9.7g of thiovalerolactam as a white solid, mp 85-88°C. To a solution of 9g (0.078mol) of thiovalerolactam in 100mL

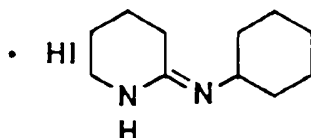
187

Filtration and ether trituration afforded 18.5g of the thio-iminoether hydroiodide salt as a white solid. To a solution of 0.2g (0.00077mol) of the thio-iminoether in 3mL of ethanol was added 0.2g (0.002mol) of trifluoroethylamine. This mixture was sealed and stirred at 25°C for eighteen hours. Evaporation of the solvent afforded the title product as a white solid. ¹H-NMR(D₂O) 1.65-1.7 (m, 4H), 2.56 (m, 2H), 3.32 (m, 2H), 3.95 (q, 2H); Mass Spectra, M+H=181.

10

EXAMPLE 311

2-(Cyclohexylimino)pentamethylenimine Hydroiodide salt



15

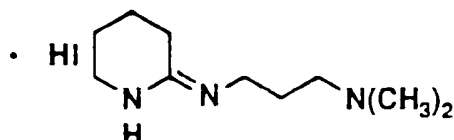
To a solution of 0.2g (0.00077mol) of the thio-iminoether from example RKW-E in 3mL of ethanol was added 0.08g (0.0008mol) of cyclohexylamine. This mixture was sealed and stirred at 25°C for eighteen hours. Evaporation of the solvent afforded the title product as a white solid. ¹H-NMR(D₂O) 1.1-1.3 (m, 6H), 1.45-1.9 (m, 10H), 2.42 (t, 2H), 3.25 (t, 3H), 3.95 (q, 2H); Mass Spectra, M+H=181.

20

EXAMPLE 312

2-(Dimethylaminopropylimino)pentamethylenimine Hydroiodide salt

5



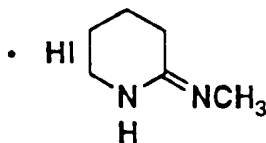
To a solution of 0.2g (0.00077mol) of the thio-iminoether from example RKW-E in 3mL of ethanol was added 0.08g (0.0008mol) of N,N-dimethylaminopropylamine. This mixture was sealed and stirred at 25°C for eighteen hours. Evaporation of the solvent afforded the title product as a white solid. ¹H-NMR(D₂O) 1.6-1.75 (m, 6H), 2.1 (s, 6H), 2.3 (dd, 2H), 2.48 (t, 2H), 3.1 (t, 2H), 3.28 (t, 2H); Mass Spectra, M+H=184.

15

EXAMPLE 313

2-(Methylimino)pentamethylenimine Hydroiodide salt

20

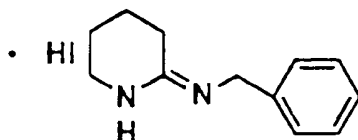


To a solution of 0.2g (0.00077mol) of the thio-iminoether from example RKW-E in 3mL of ethanol was added 2mL of ethanol saturated with anhydrous methylamine. This mixture was sealed and stirred at 25°C for eighteen hours. Evaporation of the solvent afforded the title product as a white solid. ¹H-NMR(D₂O) 1.6-1.7 (m, 4H), 2.45 (t, 2H), 2.7 (s, 3H), 3.3 (t, 2H); Mass Spectra, M+H=113.

30

EXAMPLE 314

2-(Benzylimino)pentamethylenimine Hydroiodide salt

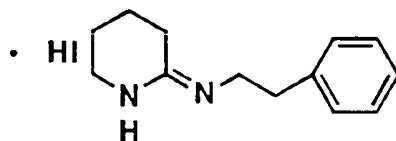


To a solution of 0.2g (0.00077mol) of the thio-iminoether from example RKW-E in 3mL of ethanol was added 0.08g (0.0008mol) of benzylamine. This mixture was sealed and stirred at 25°C for eighteen hours. Evaporation of the solvent afforded the title product as a white solid. Mass Spectra, M+H=189.

EXAMPLE 315

15

2-(Phenethylaminopropylimino)pentamethylenimine Hydroiodide salt



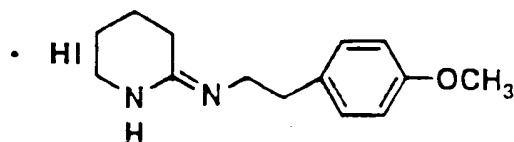
25

To a solution of 0.2g (0.00077mol) of the thio-iminoether from example RKW-E in 3mL of ethanol was added 0.09g (0.0008mol) of phenethylamine. This mixture was sealed and stirred at 25°C for eighteen hours. Evaporation of the solvent afforded the title product as a white solid. ¹H-NMR(D₂O) 1.6 (m, 4H), 2.4 (m, 2H), 2.8 (t, 2H), 3.1 (m, 2H), 3.4 (t, 2H), 7.18-7.3 (m, 5H); Mass Spectra, M+H=203.

30

EXAMPLE 316

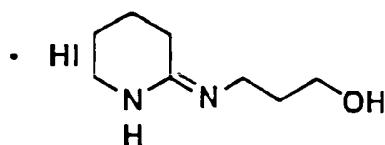
190



To a solution of 0.2g (0.00077mol) of the thio-iminoether
5 from example RKW-E in 3mL of ethanol was added 0.12g
(0.0008mol) of p-methoxyphenethylamine. This mixture was
sealed and stirred at 25°C for eighteen hours.
Evaporation of the solvent afforded the title product as a
white solid. ¹H-NMR(D₂O) 1.6 (m, 4H), 2.18 (m, 2H), 2.75
10 (t, 2H), 3.05 (m, 2H), 3.25 (t, 2H), 3.7 (s, 3H), 6.85 (d,
2H), 7.1 (d, 2H); Mass Spectra, M+H=233.

EXAMPLE 317

15 2-(3-hydroxypropylimino)pentamethylenimine Hydroiodide
salt



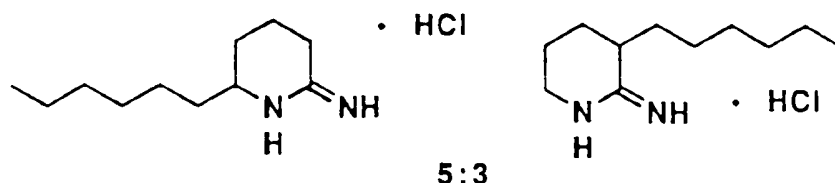
20 To a solution of 0.2g (0.00077mol) of the thio-iminoether
from example RKW-E in 3mL of ethanol was added 0.06g
(0.0008mol) of 3-hydroxypropylamine. This mixture was
sealed and stirred at 25°C for eighteen hours.
Evaporation of the solvent afforded the title product as a
25 white solid. ¹H-NMR(D₂O) 1.6-1.8 (m, 6H), 2.45 (t, 2H),
3.15 (t, 2H), 3.28 (t, 2H), 3.55 (t, 2H); Mass Spectra,
M+H=157.

EXAMPLE 318

30

(5:3) 2-Imino-6-hexyl-pentamethylenimine Hydrochloride

191



To a solution of 10g (0.06mol) of 2-hexylcyclopentanone in 80mL of ethanol and 60mL of water was added 6.3g (0.09mol) of hydroxylamine hydrochloride and 9g (0.11mol) of sodium acetate. This mixture was stirred for four hours at reflux, then for eighteen hours at 25°C. The reaction mixture was concentrated to a reduced volume, diluted with ethyl acetate, washed with three 200mL portions of aqueous NaCl, dried (MgSO₄) filtered and concentrated to afford 10.2g of the 2-hexylcyclopentanoneoxime as a colorless oil. A solution of 8g (0.044mol) of the oxime in 50mL of acetone was treated with 48.4mL (0.0484mol) of 1N NaOH at 0°C. To this stirred mixture was added 8.1g (0.046mol) of benzenesulfonyl chloride dropwise. The resulting mixture was stirred for eighteen hours at 25°C. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with aqueous NaCl, dried (MgSO₄), filtered and concentrated to afford 8g of a yellow oil. Chromatography (C-18, 10% acetonitrile/water to 70% acetonitrile/water) on 2g of the yellow oil afforded 1.5g of a 2:1 ratio of the 6-hexylvalerolactam to the 3-hexylvalerolactam. To a solution of 1.5g (0.01mol) of trimethyloxonium tetrafluoroborate in 35mL of methylene chloride was added 1.5g (0.0082mol) of the above valerolactam mixture. This mixture was stirred for 18 hours at 25°C. The reaction mixture was then diluted with ethyl acetate, washed with dilute potassium carbonate, dried (MgSO₄), filtered through a patty of silica gel and concentrated to afford 0.6g of the iminoether as a yellow oil. This oil was

reaction mixture was then concentrated to remove solvents. The residue was dissolved in water and extracted with ethyl acetate. The aqueous layer was lyophilized to afford 0.16g of a 5:3 mixture of 2-Imino-6-hexyl-

5 pentamethylenimine Hydrochloride salt to 2-Imino-3-hexyl-pentamethylenimine Hydrochloride salt as a white solid.

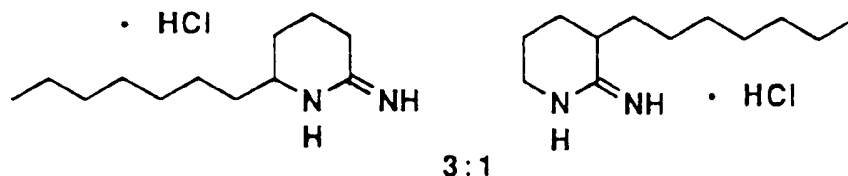
$^1\text{H-NMR}(\text{D}_2\text{O})$ 0.72 (t, 3H), 1.1-1.9 (m, 14H), 2.3-2.62 (m, 2H), 3.2 (t, 3-isomer), 3.38 (p, 6-isomer); Mass Spectra, $\text{M}+\text{H}=183$; Elemental analysis Calcd. for $\text{C}_{11}\text{H}_{23}\text{N}_2\text{Cl}_1 + 3$

10 $\text{N}_1\text{H}_4\text{Cl}_1 + 3/4 \text{H}_2\text{O}$: C, 33.64; H, 9.34; N, 17.83. Found C, 33.82, H, 9.20, N, 17.97.

EXAMPLE 319

(3:1) 2-Imino-6-heptyl-pentamethylenimine Hydrochloride salt:

5 2-Imino-3-heptyl-pentamethylenimine Hydrochloride salt

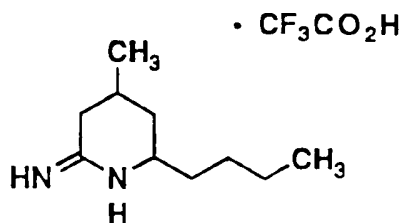


To a solution of 10g (0.055mol) of 2-heptylcyclopentanone
 10 in 75mL of ethanol and 50mL of water was added 5.8g
 (0.083mol) of hydroxylamine hydrochloride and 8.2g
 (0.1mol) of sodium acetate. This mixture was stirred for
 four hours at reflux, then for eighteen hours at 25°C.
 The reaction mixture was concentrated to a reduced volume,
 15 diluted with ethyl acetate, washed with three 200mL
 portions of aqueous NaCl, dried (MgSO₄) filtered and
 concentrated to afford 10g of the 2-
 heptylcyclopentanoneoxime as a colorless oil. A solution
 of 8g (0.04mol) the oxime in 50mL of acetone was treated
 20 with 44mL (0.044mol) of 1N NaOH at 0°C. To this stirred
 mixture was added 7.4g (0.042mol) of benzenesulfonyl
 chloride dropwise. The resulting mixture was stirred for
 eighteen hours at 25°C. The reaction mixture was poured
 into water and extracted with ethyl acetate. The organic
 25 layer was separated, washed with aqueous NaCl, dried
 (MgSO₄), filtered and concentrated to afford 8g of a
 yellow oil. Chromatography (C-18, 10% acetonitrile/water
 to 70% acetonitrile/water) on 2g of the yellow oil,
 afforded 1.1g of a mixture of the 6-heptylvalerolactam to
 30 the 3-heptylvalerolactam. To a solution of 1g (0.007mol)
 of trimethyloxonium tetrafluoroborate in 25mL of methylene
 chloride was added 1.1g (0.0056mol) of the above
 valerolactam mixture. This mixture was stirred for 18

dried (MgSO_4), filtered through a patty of silica gel and concentrated to afford 0.6g of the iminoether as a yellow oil. This oil was dissolved in 40mL of methanol and 0.17g (0.0032mol) of ammonium chloride was added. After stirring at reflux for 4 hours the mixture was stirred at 25°C for 18 hours. The reaction mixture was then concentrated to remove solvents. The residue was dissolved in water and extracted with ethyl acetate. The aqueous layer was lyophilized to afford 0.31g of a 3:1 mixture of 2-Imino-6-heptyl-pentamethylenimine Hydrochloride salt to 2-Imino-3-heptyl-pentamethylenimine Hydrochloride salt as a white solid. $^1\text{H-NMR}(\text{D}_2\text{O})$ 0.7 (t, 3H), 1.05-1.9 (m, 16H), 2.3-2.6 (m, 2H), 3.2 (t, 3-isomer), 3.35 (p, 6-isomer); Mass Spectra, $\text{M}+\text{H}=197$; Elemental analysis Calcd. for $\text{C}_{12}\text{H}_{25}\text{N}_2\text{Cl}$ + 0.6 $\text{N}_1\text{H}_4\text{Cl}$ + 1/3 H_2O : C, 53.22; H, 10.44; N, 13.45. Found C, 53.29, H, 10.53, N, 13.26.

EXAMPLE MVT-A

20 2-Imino-4-methyl-6-butyl-pentamethylenimine
Trifluoroacetic acid salt



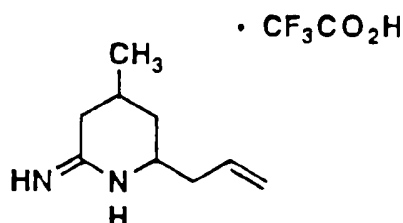
25 The title compound was prepared as in Example 319 from 3.4g of 2-butyl-4-methylcyclopentanone. A final purification by C-18 HPLC (0-40% acetonitrile/ H_2O , 30 min.) afforded 0.2g of the title compound as an oily solid. $^1\text{H-NMR}(\text{D}_2\text{O})$ 0.68-0.76 (m, 3H), 0.86 (d, $\text{J}=6\text{Hz}$, 3H), 1.12-1.24 (m, 4H), 1.28-1.76 (m, 4H), 1.92-2.16 (m, 2H), 2.46-2.58 (m, 1H), 3.40-3.50 (m, 1H); Mass Spectra,

30

EXAMPLE MVT-B

2-Imino-4-methyl-6-allyl-pentamethylenimine
Trifluoroacetic acid salt

5

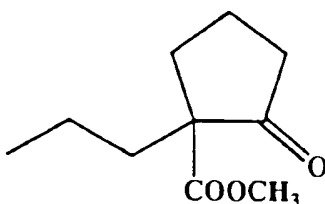


The title compound was prepared as in EXAMPLE 319, from
5.3g of 2-allyl-4-methylcyclopentanone. A final
10 purification by C-18 HPLC (0-40% acetonitrile/H₂O, 30
min.) afforded 1.2g of the title compound as an oily
solid. ¹H-NMR(D₂O) 0.80-0.92 (m, 3H), 1.40-2.88 (m, 7H),
3.20-3.65 (m, 1H), 4.96-5.16 (m, 2H), 5.60-5.78 (m, 1H);
Mass Spectra, M+H=153.

15

EXAMPLE 320

Methyl 2-(1-propyl)cyclopentanone 2-carboxylate



20

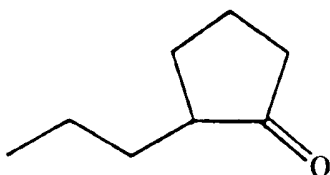
Methyl cyclopentanone 2-carboxylate (Fluka) (14.2 g, 0.1
mol), 1-iodopropane (Aldrich) (17 g, 0.1 mol), and
potassium carbonate (10 g) were stirred in 100 ml of N,N-
25 dimethylformamide (DMF) under nitrogen gas at 50 °C for 16
h. DMF was removed by rotary evaporation under reduced
pressure. The residue was suspended in 500 ml of ethyl
acetate and water (1/1 mixture). The ethyl acetate layer
was separated and washed with water, and then with sat.
30 sodium chloride solution and dried over MgSO₄. After

crude product was used for the next reaction without further purification.

EXAMPLE 321

5

2-(1-Propyl)cyclopentanone

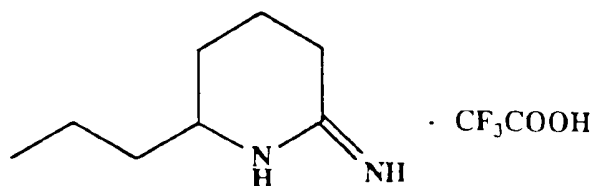


- 10 Methyl 2-(1-propyl)cyclopentanone 2-carboxylate (10 g, 0.054 mol), sodium cyanide (2.9 g, 0.06 mol) and dimethylsulfoxide (100 ml) was stirred at 1600 °C for 3 hr under nitrogen gas. After cooling, the reaction mixture was poured into ice-cooled water and extracted with 300 ml
- 15 of a mixture of ethyl ether/hexanes (1/1). The ethyl ether/hexanes layer was separated, and was washed with saturated NaCl solution twice. After drying over MgSO₄, the solvent was removed by rotary evaporation. The crude product was purified by silica gel column chromatography
- 20 with a mixture of hexanes and ethyl acetate (7/3) as eluate. The product weighed 5.5 g (83% yield). Mass Spectra: M + H = 123.

EXAMPLE 322

25

2-Imino-6-(1-propyl)-pentamethylenimine trifluoroacetate salt



30

2-Imino-6-(1-propyl)-pentamethylenimine was prepared as in example 322 from 2-propylcyclopentanone. A final purification by reverse-phased C18 HPLC (0-50%

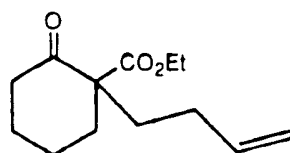
197

3H), 1.15-1.88 (m, 8H), 2.38-2.50 (m, 2H), 3.3-3.4 (m, 1H) Mass Spectra. M + H = 255.

EXAMPLE 323

5

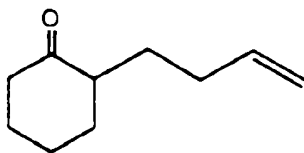
2-(1-butenyl)-2-carboethoxycyclohexanone



- 10 Sodium hydride, 60% in mineral oil (8.3 g, 200 mmol) was washed with 2 portions of hexane and then dried under an N₂ flow. This was suspended in dimethylformamide and ethyl 2-cyclohexanonecarboxylate (34.1 g, 200 mmol) was added slowly under N₂ (note the foaming and exotherm), with cooling with a
- 15 25 °C water bath. After complete addition, the mixture was stirred at 25 °C for ~1 hour and the reagents added. The stirring mixture was heated to 50 °C for 18 hours (overnight). The reaction was then cooled to room temperature. The entire mixture was poured into water, neutralized with dilute HCl and
- 20 extracted with two portions of 1:1 ether-hexane. The combined organics were then washed with two portions of water followed by saturated brine, then dried over MgSO₄, filtered and stripped giving 41.8 g of an impure mixture of products. Purification of the product by chromatography (silica gel, : 5
- 25 % methyl t-butyl ether / 90 % hexane) gave 28.4 g of the title compound.

EXAMPLE 324

2-(1-butenyl)cyclohexanone

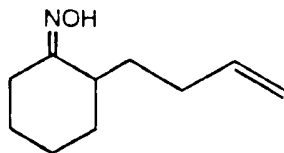


5
The reagents (1-butenyl)-2-carboethoxy cyclohexanone (11.2 g, 50 mmol), lithium chloride (10.6 g, 250 mmol), water (0.99 g, 55mmol), and dimethyl sulfoxide, (250 ml) were
10 combined under N₂ and refluxed for 2 hours. The reaction was then cooled to 25 °C. The reaction mixture was poured into water and extracted with two portions of 1:1 ether - hexane. The organic phases were combined and washed with two portions water followed by saturated brine and then
15 dried over MgSO₄. After filtering and stripping, the product was purified by fractional distillation at 1.5 mm Hg. (The product boils at 65 to 70 °C at 1 to 2 mm Hg.), giving 5.5 g of the desired title ketone.

20

EXAMPLE 325

2-(1-butenyl)cyclohexanone, oxime



25

2-(1-butenyl)cyclohexanone from example 324 (7.70 g, 51 mmol) was converted to the title compound by the method of Example 24 using 5.3 g (76 mmol) of hydroxylamine

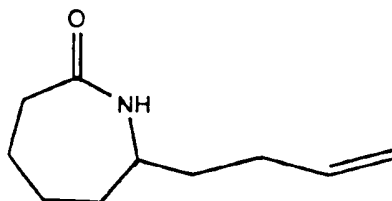
199

70 mL of EtOH and 70 mL of water. The procedure produced 8.48 g of the title material as a white solid.

EXAMPLE 326

5

hexahydro-7-(1-butenyl)-1H-azepin-2-one

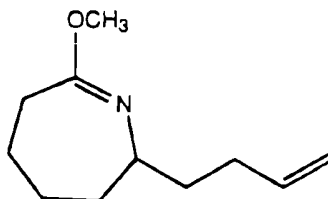


The title compound of EXAMPLE 325 was converted to the present title compound by the method of EXAMPLE 29.

EXAMPLE 327

15

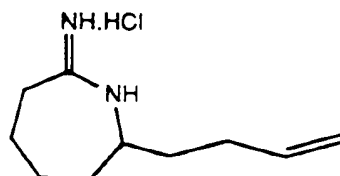
4,5,6,7-tetrahydro-2-methoxy-7-(1-butenyl)-3H-azepine



The product of Example 326 (1.34 g, 8 mmol) was reacted with trimethyloxonium tetrafluoroborate (1.63 g, 11 mmol) by the method of Example 26 to yield 1.5 g (100%) of the title material.

EXAMPLE 328

hexahydro-7-(1-butenyl)-1H-azepin-2-imine, monohydrochloride



The product of Example 327 (1.5 g, 8 mmol) in 85 mL of MeOH was reacted with ammonium chloride (0.36 g, 6.8 mmol) by the method of Example 27 to yield 1.4 g (83%) of the title material.

Elemental analysis: $C_{10}H_{17}N_2 \cdot HCl \cdot 0.45 H_2O$ (MW = 210.83)

	C	H	N	Cl
15 Calculated:	56.97	9.51	13.39	16.82
Found:	57.02	9.34	13.16	16.86

1H NMR (D₂O): δ 5.75-5.95 (m, 1H), 5.1 (m, 2H), 3.65 (tt, 1H) 2.75-2.5 (m, 2H), 2.3 (m, 2H), 2.05-1.3 (m, 8H)

Biological Data

The activity of the above listed compounds as NO synthase inhibitors has been determined in the following assays:

Citrulline Assay for Nitric Oxide Synthase

Nitric oxide synthase activity was measured by monitoring the conversion of [3H]-arginine to [3H]-citrulline. Mouse inducible nitric oxide synthase (iNOS) was prepared from an extract of LPS-treated RAW 264 cells and assayed

from an extract of rat cerebellum and partially purified by DEAE-Sepharose chromatography. Enzyme and inhibitors were incubated at 37°C for 15 minutes in a reaction volume of 100 mL with the following components added to start the reaction: 50 mM Tris (pH 7.6), 1 mg/ml bovine serum albumin, 1 mM DTT, 2 mM CaCl_2 , 10 mM FAD, 10 mM tetrahydrobiopterin, 30 mM L-arginine containing L-[2,3- ^3H]-arginine at 300 cpm/pmole and 1 mM NADPH. For constitutive NOS, 50 nM calmodulin was also added. The reaction was terminated by addition of cold stop buffer containing 10 mM EGTA, 100 mM HEPES, pH 5.5 and 1 mM citrulline. [^3H]-Citrulline was separated by chromatography on Dowex 50W X-8 cation exchange resin and radioactivity determined with a liquid scintillation counter.

Raw Cell Nitrite Assay

RAW 264.7 cells are plated to confluency on a 96-well tissue culture plate grown overnight (17h) in the presence of LPS to induce NOS. A row of 3-6 wells were left untreated and served as controls for subtraction of nonspecific background. The media was removed from each well and the cells are washed twice with Krebs-Ringers-Hepes (25mM, pH 7.4) with 2 mg/ml glucose. The cells are then placed on ice and incubated with 50 mL of buffer containing L-arginine (30 mM) +/- inhibitors for 1h. The assay is initiated by warming the plate to 37°C in a water bath for 1h. Production of nitrite by intracellular iNOS is linear with time. To terminate the cellular assay, the plate of cells is placed on ice and the nitrite-containing buffer removed and analyzed for nitrite using a previously published fluorescent determination for nitrite. T.P. Misko et al. Analytical Biochemistry, 214, 11-16 (1993). All values are the average of triplicate wells and are compared to a background-subtracted induced set of cells

202

TABLE I

	<u>Compound</u>	<u>iNOS</u>	<u>cNOS</u>	<u>Raw Cell</u>
			IC ₅₀ (μM)	IC ₅₀ (μM)
5				
	Example 1	2.1	13.3	60
	Example 2	2.2		9.9
				>1000
10	Example 3	43% * 10 μM		
	Example 4	4.6		2.4
				14
	Example 5	3.2		9.4
				18
15	Example 6	0.055		0.285
	Example 7	2.0		13.3
20	Example 8	0.16		0.99
	Example 9	1.496		2.01
	Example 10	0.043		0.127
25	Example 11	0.92		2.768
	Example 12	5.1		32
				1.8
30	Example 13	0.6		2.0
				14
	Example 14	5.0		23
				>1000
	Example 15	8% @ 10 μM		
35	Example 16	0.8		4.0
				4.3

TABLE I (cont.)

	<u>Compound</u>	<u>iNOS</u>	<u>eNOS</u> IC ₅₀ [μM]	<u>Raw Cell</u> IC ₅₀ [μM]
5	Example 17	0.8	2.7	28
	Example 18	0.8	6.0	6.0
10	Example 19	42% @ 10 μM		
	Example 20	1.0	5.0	160
	Example 21	40	500	>1000
15	Example 22	30	1300	>1000
	Example 23	41% @ 10 μM		
20	Example 60	1.1	32	3.5
	Example 70	5.9	32	24
	Example 90	7.0	46	
25	Example 96	9.3	1405	
	Example 107	3.8	342	15
30	Example 108	0.14	19	0.57
	Example 114	0.081	7.8	0.55
	Example 173	42% @ 10 μM	49% @ 10 μM	
35	Example 164	60% @ 100 μM	74% @ 100 μM	

TABLE I (cont.)

	<u>Compound</u>	<u>iNOS</u>	<u>cNOS</u> IC ₅₀ [μM]	<u>Raw Cell</u> IC ₅₀ [μM]
5	Example 170	3.4	53	
	Example 182	1.4	14	
10	Example 188	0.55	106	0.65
	Example 192	12	179	31
15	Example 198	2.1	652	3.3
	Example 217	0.17	1.6	0.25

In Vivo Assay

Rats were treated with an intraperitoneal injection of 10mg/kg of endotoxin (LPS) with or without oral administration of the nitric oxide synthase inhibitors. Plasma nitrites were measured 5 hours post-treatment. The results show that the administration of the nitric oxide synthase inhibitor decreases the rise in plasma nitrites, a reliable indicator of the production of nitric oxide, induced by endotoxin.

IP is the abbreviation for 2-iminopiperidine.
LPS is the abbreviation for endotoxin

TABLE II

ED50's for Homoiminopiperidines determined in the Low
Endotoxin in Rat Model

All compounds administered p.o. unless otherwise noted

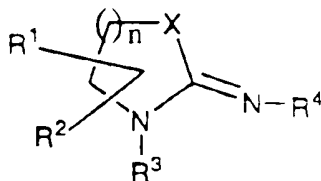
<u>Compound</u>	<u>ED50 (mg/kg)</u>
96	3.8
108	3.7
114	3.4
188	3.7
198	5.0* (determined using iv infusion)

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a compound having the formula:

5



and salts, pharmaceutically acceptable esters and prodrugs thereof, wherein:

10

X is selected from the group consisting of methylene, nitrogen, oxygen, S, SO, and SO₂ wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;

n = 0 to about 7;

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon, -CONR⁵R⁶, -SO₂NR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals can be optionally substituted with one or more of the following:

30

hydroxy, lower alkyl, lower alkenyl, lower alkynyl,
lower alkoxy, lower thioalkoxy, halogen, nitro, amino,

wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

5

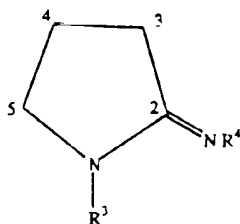
and R^1 , R^2 , may optionally together form an alicyclic hydrocarbon, heterocycle or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

10 lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R^3 , R^4 are independently selected from the group
15 consisting of hydrogen, hydroxy, and alkyloxy;

R^5 and R^6 are independently selected from the group consisting of hydrogen, lower alkyl, and aryl;

20 with the proviso that when $n=1$



and R^1 and/or R^2 are at position 3 or 4, neither R^1 or R^2
25 is aryl; and

together with at least one non-toxic pharmaceutical acceptable carrier.

30 2. The pharmaceutical composition as recited in Claim 1 wherein:

n is an integer 0 to 5;

R^1 and R^2 , are independently selected from the group
5 consisting of hydrogen, hydroxy, lower alkyl, lower
alkenyl, lower alkynyl, haloalkyl, aromatic hydrocarbon
and alicyclic hydrocarbon wherein all said radicals are
optionally substituted with one or more of the following:
10 carboxyl, carboalkoxy, amino, lower alkoxy, lower
thioalkoxy and lower alkyl wherein all said substitutions
may be optionally substituted with one or more of the
following: amino, carboxyl, and carboalkoxy ;

and R^1 , R^2 , may optionally together form an alicyclic
15 hydrocarbon or aromatic hydrocarbon; and

R^3 , R^4 are independently selected from the group
consisting of hydrogen and hydroxy.

20 3. The pharmaceutical composition as recited in
Claim 1 wherein:

X is selected from the group consisting of methylene,
nitrogen, oxygen, and sulfur;

25 n is an integer from 0 to 5;

R^1 and R^2 are independently selected from the group
consisting of hydrogen, hydroxy, lower alkyl, lower
30 alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl,
cyano, sulfonyl, and haloalkyl wherein all said radicals
may optionally be substituted with hydroxy, lower alkyl,
lower alkoxy, halogen, nitro, amino, carboxyl, cyano,
sulfonyl, and haloalkyl groups and R^1 , R^2 may optionally
35 together form an alicyclic, heterocyclic or aromatic
radical.

Claim 1 wherein:

X is methylene, nitrogen, oxygen, or sulfur wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;

n is an integer from 0 to 4;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl of 1 to about 6 carbon atoms, lower alkoxy of 1 to about 6 carbon atoms, lower thioalkoxy of 1 to about 6 carbon atoms, lower alkenyl of 1 to about 6 carbon atoms, lower alkynyl of 1 to about 6 carbon atoms, halogen, nitro, amino, carboxyl, cyano, sulfonyl, trifluoroalkyl and haloalkyl and wherein each said radical may optionally be substituted with hydroxy, lower alkyl of 1 to about 6 carbon atoms, lower alkoxy of 1 to 4 carbon atoms, lower alkenyl of 1 to about 6 carbon atoms, lower alkynyl of 1 to about 6 carbon atoms, halogen, nitro, amino, carboxyl, cyano, sulfonyl, and haloalkyl groups and R^1 , R^2 may optionally together form a 3 to 7-carbon membered alicyclic, heterocyclic or aromatic radical.

5. The pharmaceutical compositions as recited in Claim 1 wherein:

X is methylene, nitrogen, oxygen, or sulfur;

n is an integer from 0 to 4; are

R¹ and R² are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl of 1 to 3 carbon atoms, nitro, amino, carboxyl, and cyano and wherein all said radicals may optionally be substituted with hydroxy, lower alkyl of 1 to 3 carbon atoms, lower alkoxy of 1 to 3 carbon atoms, lower thioalkoxy of 1 to 3 carbon atoms, halogen, nitro, amino, carboxy and cyano and R¹, R² may optionally together form a 3 to 7-carbon membered alicyclic, heterocyclic or aromatic ring.

6. The pharmaceutical composition as recited in Claim 1 wherein:

X is lower alkyl, nitrogen, oxygen, or sulfur;

n is an integer from 0 to 4; and

R¹ and R² are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl of 1 to 3 carbon atoms, amino, and carboxyl and wherein all said radicals may optionally be substituted with hydroxy, lower alkyl of 1 to 3 carbon atoms, lower alkoxy of 1 to 3 carbon atoms, amino, lower thioalkoxy of 1 to 3 carbon atoms and carboxy.

7. The pharmaceutical composition as defined in Claim 1 wherein the compound is selected from the group consisting of 2-Imino-octamethyleneimine, 2-Imino-heptamethyleneimine, 2-Imino-6-methyltetramethyleneimine, 2-Imino-5-methyltetramethyleneimine, 2-Iminopyrrolidine, 2-

- thiapiperidine, 2-Imino-3-oxopiperidine, 2-Iminooxazolidine, 5-Chloromethyl-2-iminooxazolidine, 2-Iminobiotin, 2-Iminobiotin ethyl ester, or 1-Methyl-2-iminotetrahydropyrimidine, 3,4,5,6,7,8-hexahydro-2[¹H]-quinolineimine, 2-Imino-4-
- 5 methylpiperidine, 2-Imino-5-methylpiperidine, 2-Imino-6-methylpiperidine, 2-Imino-3-methylpiperidine, 2-Imino-4,6-dimethylpiperidine, 2-Imino-3-hydroxypiperidine, hexahydro-3,7-dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-3-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-7-
- 10 methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-4-(trifluoromethyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-6-(trifluoromethyl)-1H-azepin-2-imine, monohydrochloride; 7-ethyl-hexahydro-1H-azepin-2-one, mixture with 3-ethyl-hexahydro-1H-azepin-2-one, hexahydro-3,7-
- 15 dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-3-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-7-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-4-(trifluoromethyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-6-(trifluoromethyl)-1H-azepin-2-imine,
- 20 monohydrochloride; 7-ethyl-hexahydro-1H-azepin-2-imine, monohydrochloride 7-ethyl-hexahydro-1H-azepin-2-imine, monohydrochloride; 3-ethyl-hexahydro-1H-azepin-2-imine, monohydrochloride; hexahydro-6,6-dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-4,4-dimethyl-1H-azepin-2-imine,
- 25 monohydrochloride; hexahydro-5-methyl-1H-azepin-2-imine, monohydrochloride; 5-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride; hexahydro-5-(1-methylethyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-5-pentyl-1H-azepin-2-imine, monohydrochloride; 5-(1,1-dimethylethyl)-hexahydro-
- 30 1H-azepin-2-imine, monohydrochloride; hexahydro-4R-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-6R-methyl-1H-azepin-2-imine, monohydrochloride; 3-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride; 7-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride; 3-(1,1-dimethylethyl)-
- 35 hexahydro-1H-azepin-2-imine, monohydrochloride; 7-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-imine,

- 2-imine, monohydrochloride;
hexahydro-3-propyl-1H-azepin-2-imine, monohydrochloride;
hexahydro-7-propyl-1H-azepin-2-imine, monohydrochloride;
hexahydro-3-(1-methylpropyl)-1H-azepin-2-imine,
5 monohydrochloride; hexahydro-7-(1-methylpropyl)-1H-azepin-
2-imine, monohydrochloride; hexahydro-3,6-dimethyl-1H-
azepin-2-imine, monohydrochloride; 4,5,6,7-tetrahydro-4,7-
dimethyl-3H-azepin-2-amine, monohydrochloride; (7S-trans)-
hexahydro-7-(1-methylethyl)-4-methyl-1H-azepin-2-imine,
10 monohydrochloride; (3S-trans)-hexahydro-3-(1-methylethyl)-
6-methyl-1H-azepin-2-imine, monohydrochloride; 4R-
methylpiperidin-2-imine, monohydrochloride; 5R-
methylpiperidin-2-imine, monohydrochloride; 4-
ethylpiperidin-2-imine, monohydrochloride; 5-
15 ethylpiperidin-2-imine, monohydrochloride; 6-
ethylpiperidin-2-imine, monohydrochloride; 3-
ethylpiperidin-2-imine, monohydrochloride; 6,6-
dimethylpiperidin-2-imine, monohydrochloride; 3,3-
dimethylpiperidin-2-imine, monohydrochloride; 1,2,3,4-
20 tetrahydroquinolin-2-imine, monohydrochloride; 2,3,4,5-
tetrahydro-1H-1-benzazepin-2-imine, monohydrochloride;
4,4-dimethylpiperidin-2-imine, monohydrochloride; (trans)-
octahydro-1H-isoindol-1-imine, monohydrochloride; 2-
azabicyclo[3.2.1]octan-3-imine, monohydrochloride, mixture
25 with 3-azabicyclo[3.2.1]octan-2-imine, monohydrochloride;
4-methylpyrrolidin-2-imine, monohydrochloride; 3-
butylhexahydro-1H-azepin-2-imine, monohydrochloride; 7-
butylhexahydro-1H-azepin-2-imine, monohydrochloride;
hexahydro-7-phenyl-1H-azepin-2-imine, monohydrochloride;
30 3-(2-ethylbutyl)hexahydro-1H-azepin-2-imine,
monohydrochloride; 7-(2-ethylbutyl)hexahydro-1H-azepin-2-
imine, monohydrochloride; hexahydro-7-imino-1H-azepine-2-
ethanol, monohydrochloride; hexahydro-7-imino-1H-azepine-
2-acetic acid, monohydrochloride; methyl hexhydro-7-imino-
35 1H-azepine-2-acetate, monohydrochloride; octahydro-3-(2-
propenyl)azocin-2-imine, monohydrochloride; octahydro-3-

methylpyrrolidin-2-imine, monohydrochloride; 5S-(methoxymethyl)pyrrolidin-2-imine, monohydrochloride; 5R-(methoxymethyl)pyrrolidin-2-imine, monohydrochloride; ethyl 5-iminopyrrolidine-2S-acetate, monohydrochloride;

5 methyl 3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]-2S-[[[(phenylmethoxy)carbonyl]

amino]propanoate, monohydrochloride; methyl 2S-amino-3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]propanoate,

dihydrochloride; 3-(7-iminoazepin-2-yl)-1,2-propanediol,

10 monohydrochloride; ethyl α-amino-5-imino-3-methylpyrrolidine-2-pentanoate, dihydrochloride; ethyl α-amino-7-imino-γ-methoxy-1H-azepine-2-pentanoate,

dihydrochloride; ethyl 2-amino-5-(hexahydro-7-oxo-1H-azepin-2-yl)-3-pentenoate, monohydrochloride; ethyl α-

15 amino-hexahydro-7-oxo-1H-azepine-2-pentanoate, monohydrochloride; ethyl hexahydro-7-imino-α

[[[(phenylmethoxy)carbonyl]amino]-1H-azepine-2-pentanoate, monohydrochloride; ethyl α-amino-hexahydro-7-imino-1H-

azepine-2-pentanoate, dihydrochloride; 7-(cyclohexen-1-

20 yl)hexahydro-1H-azepin-2-imine, monohydrochloride; 7-(2-butynyl)hexahydro-1H-azepin-2-imine, monohydrochloride; 4-[1-amino-4-(5-imino-3-methylpyrrolidin-2-yl)butyl]-1,3-dioxolan-2-one, dihydrochloride; 4-methyl-5-(2-propenyl)pyrrolidin-2-imine, monohydrochloride; 4-[1-

25 amino-4-(hexahydro-7-imino-1H-azepin-2-yl)butyl]-1,3-dioxolan-2-one, dihydrochloride; 2S-amino-3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]propanoic acid,

dihydrochloride; 3-ethoxy-2-imino-6-methylpiperidine hydrochloride; 5-amino-2-iminopiperidine hydrochloride; 2-

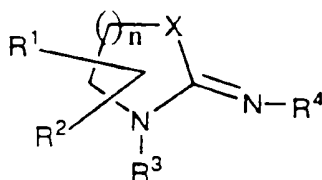
30 imino-4-piperidine carboxylic acid hydrochloride; 5-amino-2-imino-4-methylpiperidine dihydrochloride (cis and trans isomers); Ethyl (2'-imino)-2-(3'-(piperidineoxy)

acetate hydrochloride; 2-imino-5-(trifluoromethyl)piperidine hydrochloride; 5-aminomethyl-2-imino-4,6-

35 dimethylpiperidine dihydrochloride; 2-imino-6-methyl-4-(trifluoromethyl)piperidine hydrochloride; 2-imino-4-

(trifluoromethyl)piperidine hydrochloride; 2-(N,N-dimethylamino)-4-methyl-3,4,5,6-tetrahydropyridine hydrochloride; 2'-(2-aminoethylimino)-5'-(trifluoromethyl)piperidine dihydrochloride; 6-Benzyl-2-
 5 iminopiperidine hydrochloride; 2-(cyclohexylmethyl)-6-iminopiperidine hydrochloride; 2-cyclohexyl-6-iminopiperidine hydrochloride; and 4-methyl-2-(propylimino)piperidine hydrochloride.

- 10 8. A method of inhibiting nitric oxide synthesis in a subject in need of such inhibition by administering a therapeutically effective amount of a compound having the formula:



15

and salts, pharmaceutically acceptable esters and prodrugs thereof, wherein:

- 20 X is selected from the group consisting of methylene, nitrogen, oxygen, S, SO, and SO₂ wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;

25

n = 0 to about 7;

- 30 R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, allyl, aryl, alkyl, heterocyclic, aromatic hydroxy, and

sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals can be optionally substituted with one or more of the following:

5

hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, haloalkyl, $-SO_2NR^5R^6$ and $-SO_2R^5$

10 wherein all said substitutions may be optionally substituted with one or more of the following:
amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

15 and R^1 , R^2 , may optionally together form an alicyclic hydrocarbon, heterocycle or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

20 lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R^3 , R^4 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy;

25

R^5 and R^6 are independently selected from the group consisting of hydrogen, lower alkyl, and aryl.

9. The method of inhibiting nitric oxide synthesis
30 as recited in claim 8 wherein;

X is selected from the group consisting of methylene, nitrogen, oxygen, S, SO, and SO_2 wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy,
35 amino, and haloalkyl groups;

n = 0 to about 7.

R^1 and R^2 , are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon, -CONR⁵R⁶, -SO₂NR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals can be optionally substituted with one or more of the following:

hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, haloalkyl, -SO₂NR⁵R⁶ and -SO₂R⁵ wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

and R^1 , R^2 , may optionally together form an alicyclic hydrocarbon, heterocycly or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

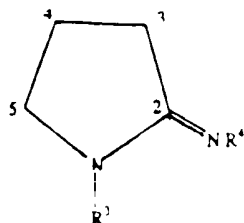
lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R^3 , R^4 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy;

R^5 and R^6 are independently selected from the group consisting of hydrogen, lower alkyl, and aryl;

with the proviso that when $n=1$

217



and R¹ and/or R² are at position 3 or 4, neither R¹ or R² is aryl.

5

10. The method of inhibiting nitric oxide synthesis as recited in claim 8 wherein;

X is selected from the group consisting of methylene, nitrogen, oxygen and sulfur;

10

n is an integer 0 to 5;

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, haloalkyl, aromatic hydrocarbon and alicyclic hydrocarbon wherein all said radicals are optionally substituted with one or more of the following: carboxyl, carboalkoxy, amino, lower alkoxy, lower thioalkoxy and lower alkyl wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, and carboalkoxy ;

15

20

and R¹, R², may optionally together form an alicyclic hydrocarbon or aromatic hydrocarbon; and

25

R³, R⁴ are independently selected from the group consisting of hydrogen and hydroxy.

11. The method of inhibiting nitric oxide synthesis as recited in claim 8 wherein;

30

n is an integer from 0 to 5;

R^1 and R^2 are independently selected from the group
5 consisting of hydrogen, hydroxy, lower alkyl, lower
alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl,
cyano, sulfonyl, and haloalkyl wherein all said radicals
may optionally be substituted with hydroxy, lower alkyl,
10 lower alkoxy, halogen, nitro, amino, carboxyl, cyano,
sulfonyl, and haloalkyl groups and R^1 , R^2 may optionally
together form an alicyclic, heterocyclic or aromatic
radical.

15 12. The method of inhibiting nitric oxide synthesis
as recited in claim 8 wherein;

X is methylene, nitrogen, oxygen, or sulfur wherein
nitrogen and lower alkyl radicals may optionally be
20 substituted with hydroxy, lower alkyl, lower alkoxy,
amino, and haloalkyl groups;

n is an integer from 0 to 4;

25 R^1 and R^2 are independently selected from the group
consisting of hydrogen, hydroxy, lower alkyl of 1 to about
6 carbon atoms, lower alkoxy of 1 to about 6 carbon atoms,
lower thioalkoxy of 1 to about 6 carbon atoms, lower
alkenyl of 1 to about 6 carbon atoms, lower alkynyl of 1
30 to about 6 carbon atoms, halogen, nitro, amino, carboxyl,
cyano, sulfonyl, trifluoroalkyl and haloalkyl and wherein
each said radical may optionally be substituted with
hydroxy, lower alkyl of 1 to about 6 carbon atoms, lower
alkoxy of 1 to 4 carbon atoms, lower alkenyl of 1 to about
35 6 carbon atoms, lower alkynyl of 1 to about 6 carbon
atoms, halogen, nitro, amino, carboxyl, cyano, sulfonyl,

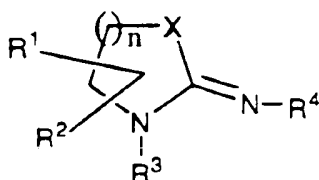
- Iminopiperidine, 2-Iminotetrahydropyrimidine, 2-Iminoimidazolidine, 2-Iminothiazolidine, 2-Imino-3-thiapiperidine, 2-Imino-3-oxopiperidine, 2-Iminooxazolidine, 5-Chloromethyl-2-iminooxazolidine, 2-Iminobiotin, 2-Iminobiotin
- 5 ethyl ester, or 1-Methyl-2-iminotetrahydropyrimidine, 3,4,5,6,7,8-hexahydro-2[¹H]-quinolineimine, 2-Imino-4-methylpiperidine, 2-Imino-5-methylpiperidine, 2-Imino-6-methylpiperidine, 2-Imino-3-methylpiperidine, 2-Imino-4,6-dimethylpiperidine, 2-Imino-3-hydroxypiperidine, hexahydro-
- 10 3,7-dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-3-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-7-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-4-(trifluoromethyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-6-(trifluoromethyl)-1H-azepin-2-imine,
- 15 monohydrochloride; 7-ethyl-hexahydro-1H-azepin-2-one, mixture with 3-ethyl-hexahydro-1H-azepin-2-one; hexahydro-3,7-dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-3-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-7-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-4-
- 20 (trifluoromethyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-6-(trifluoromethyl)-1H-azepin-2-imine, monohydrochloride; 7-ethyl-hexahydro-1H-azepin-2-imine, monohydrochloride 7-ethyl-hexahydro-1H-azepin-2-imine, monohydrochloride; 3-ethyl-hexahydro-1H-azepin-2-imine,
- 25 monohydrochloride; hexahydro-6,6-dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-4,4-dimethyl-1H-azepin-2-imine, monohydrochloride; hexahydro-5-methyl-1H-azepin-2-imine, monohydrochloride; 5-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride; hexahydro-5-(1-methylethyl)-1H-azepin-2-
- 30 imine, monohydrochloride; hexahydro-5-pentyl-1H-azepin-2-imine, monohydrochloride; 5-(1,1-dimethylethyl)-hexahydro-1H-azepin-2-imine, monohydrochloride; hexahydro-4R-methyl-1H-azepin-2-imine, monohydrochloride; hexahydro-6R-methyl-1H-azepin-2-imine, monohydrochloride; 3-cyclohexyl-hexahydro-1H-
- 35 azepin-2-imine, monohydrochloride; 7-cyclohexyl-hexahydro-1H-azepin-2-imine, monohydrochloride; 3-(1,1-dimethylethyl)-

- monohydrochloride; hexahydro-3-(2-propenyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-7-(2-propenyl)-1H-azepin-2-imine, monohydrochloride;
- hexahydro-3-propyl-1H-azepin-2-imine, monohydrochloride;
- 5 hexahydro-7-propyl-1H-azepin-2-imine, monohydrochloride;
- hexahydro-3-(1-methylpropyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-7-(1-methylpropyl)-1H-azepin-2-imine, monohydrochloride; hexahydro-3,6-dimethyl-1H-azepin-2-imine, monohydrochloride; 4,5,6,7-tetrahydro-4,7-
- 10 dimethyl-3H-azepin-2-amine, monohydrochloride; (7S-trans)-hexahydro-7-(1-methylethyl)-4-methyl-1H-azepin-2-imine, monohydrochloride; (3S-trans)-hexahydro-3-(1-methylethyl)-6-methyl-1H-azepin-2-imine, monohydrochloride; 4R-methylpiperidin-2-imine, monohydrochloride; 5R-
- 15 methylpiperidin-2-imine, monohydrochloride; 4-ethylpiperidin-2-imine, monohydrochloride; 5-ethylpiperidin-2-imine, monohydrochloride; 6-ethylpiperidin-2-imine, monohydrochloride; 3-ethylpiperidin-2-imine, monohydrochloride; 6,6-
- 20 dimethylpiperidin-2-imine, monohydrochloride; 3,3-dimethylpiperidin-2-imine, monohydrochloride; 1,2,3,4-tetrahydroquinolin-2-imine, monohydrochloride; 2,3,4,5-tetrahydro-1H-1-benzazepin-2-imine, monohydrochloride; 4,4-dimethylpiperidin-2-imine, monohydrochloride; (trans)-
- 25 octahydro-1H-isoindol-1-imine, monohydrochloride; 2-azabicyclo[3.2.1]octan-3-imine, monohydrochloride, mixture with 3-azabicyclo[3.2.1]octan-2-imine, monohydrochloride; 4-methylpyrrolidin-2-imine, monohydrochloride; 3-butylhexahydro-1H-azepin-2-imine, monohydrochloride; 7-
- 30 butylhexahydro-1H-azepin-2-imine, monohydrochloride; hexahydro-7-phenyl-1H-azepin-2-imine, monohydrochloride; 3-(2-ethylbutyl)hexahydro-1H-azepin-2-imine, monohydrochloride; 7-(2-ethylbutyl)hexahydro-1H-azepin-2-imine, monohydrochloride; hexahydro-7-imino-1H-azepine-2-
- 35 ethanol, monohydrochloride; hexahydro-7-imino-1H-azepine-2-acetic acid, monohydrochloride; methyl hexhydro-7-imino-

- (2-propenyl)azocin-2-imine, monohydrochloride; 4-ethylpyrrolidin-2-imine, monohydrochloride; 5-ethyl-4-methylpyrrolidin-2-imine, monohydrochloride; 5S-(methoxymethyl)pyrrolidin-2-imine, monohydrochloride; 5R-(methoxymethyl)pyrrolidin-2-imine, monohydrochloride; ethyl 5-iminopyrrolidine-2S-acetate, monohydrochloride; methyl 3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]-2S-[[[(phenylmethoxy)carbonyl]amino]propanoate, monohydrochloride; methyl 2S-amino-3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]propanoate, dihydrochloride; 3-(7-iminoazepin-2-yl)-1,2-propanediol, monohydrochloride; ethyl α amino 5 imino 3 methylpyrrolidine-2-pentanoate, dihydrochloride; ethyl α amino-7-imino- γ -methoxy-1H-azepine-2-pentanoate, dihydrochloride; ethyl 2-amino-5-(hexahydro-7-oxo-1H-azepin-2-yl)-3-pentenoate, monohydrochloride; ethyl α aminohexahydro-7-oxo-1H-azepine-2-pentanoate, monohydrochloride; ethyl hexahydro-7-imino- α [[[(phenylmethoxy)carbonyl]amino]-1H-azepine-2-pentanoate, monohydrochloride; ethyl α aminohexahydro-7-imino-1H-azepine-2-pentanoate, dihydrochloride; 7-(cyclohexen-1-yl)hexahydro-1H-azepin-2-imine, monohydrochloride; 7-(2-butynyl)hexahydro-1H-azepin-2-imine, monohydrochloride; 4-[1-amino-4-(5-imino-3-methylpyrrolidin-2-yl)butyl]-1,3-dioxolan-2-one, dihydrochloride; 4-methyl-5-(2-propenyl)pyrrolidin-2-imine, monohydrochloride; 4-[1-amino-4-(hexahydro-7-imino-1H-azepin-2-yl)butyl]-1,3-dioxolan-2-one, dihydrochloride; 2S-amino-3-[[[(5-iminopyrrolidin-2S-yl)methyl]oxy]propanoic acid, dihydrochloride; 3-ethoxy-2-imino-6-methylpiperidine hydrochloride; 5-amino-2-iminopiperidine hydrochloride; 2-imino-4-piperidine carboxylic acid hydrochloride; 5-amino-2-imino-4-methylpiperidine dihydrochloride (cis and trans isomers); Ethyl (2'-imino)-2-(3'-(piperidineoxy)acetate hydrochloride; 2-imino-5-(trifluoromethyl)piperidine hydrochloride; 5-aminomethyl-2-imino-4,6-

(trifluoromethyl)piperidine hydrochloride; 2-imino-3-(trifluoromethyl)piperidine hydrochloride; 2-imino-6-(trifluoromethyl)piperidine hydrochloride; 2-(N,N-dimethylamino)-4-methyl-3,4,5,6-tetrahydropyridine
 5 hydrochloride; 2'-(2-aminoethylimino)-5'-(trifluoromethyl)piperidine dihydrochloride; 6-Benzyl-2-iminopiperidine hydrochloride; 2-(cyclohexylmethyl)-6-iminopiperidine hydrochloride; 2-cyclohexyl-6-iminopiperidine hydrochloride; and 4-methyl-2-(propylimino)piperidine hydrochloride.

16. A method of selectively inhibiting nitric oxide synthesis produced by inducible NO synthase over NO produced by the constitutive forms of NO synthase in a
 15 subject in need of such inhibition by administering a therapeutically effective amount of a compound having the formula:



20

and salts, pharmaceutically acceptable esters and prodrugs thereof, wherein:

25 X is selected from the group consisting of methylene, nitrogen, oxygen, S, SO, and SO₂ wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;

30

n = 0 to about 7;

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower

halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon, -CONR⁵R⁶, -SO₂NR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals can be optionally substituted with one or more of the following:

hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, haloalkyl, -SO₂NR⁵R⁶ and -SO₂R⁵ wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

and R¹, R², may optionally together form an alicyclic hydrocarbon, heterocycly or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

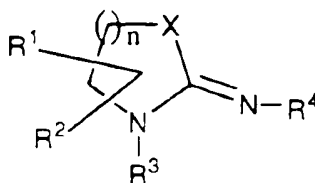
R³, R⁴ are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy;

R⁵ and R⁶ are independently selected from the group consisting of hydrogen, lower alkyl, and aryl.

17. A method of selectively inhibiting nitric oxide synthesis produced by inducible NO synthase over nitric oxide produced by the constitutive forms of NO synthase, comprising administering to a subject a therapeutically effective amount of a compound of the formula:

pharmaceutical composition as recited in claims
1,2,3,4,5,6 and 7.

- 5 18. A method of lowering nitric oxide levels
in a subject in need of such by administering a
therapeutically effective amount of a compound having the
formula:



10

and salts, pharmaceutically acceptable esters and prodrugs
thereof, wherein:

- 15 X is selected from the group consisting of methylene,
nitrogen, oxygen, S, SO, and SO₂ wherein nitrogen and
lower alkyl radicals may optionally be substituted with
hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl
groups;

20

n = 0 to about 7;

- R¹ and R², are independently selected from the group
consisting of hydrogen, hydroxy, lower alkyl, lower
25 alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy,
halogen, nitro, amino, carboxyl, cyano, sulfonyl,
haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy,
alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon,
-CONR⁵R⁶, -SO₂NR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl
30 sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate,
aryl sulfate, and sulfonamide, wherein all said radicals
can be optionally substituted with one or more of the
following:

hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy, haloalkyl, $-SO_2NR^5R^6$ and $-SO_2R^5$

5 wherein all said substitutions may be optionally substituted with one or more of the following: amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

10 and R^1 , R^2 , may optionally together form an alicyclic hydrocarbon, heterocycle or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

15 lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

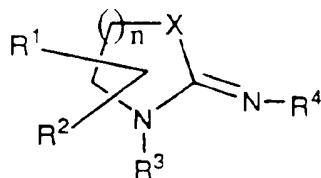
R^3 , R^4 are independently selected from the group consisting of hydrogen, hydroxy, and alkyloxy;

20

R^5 and R^6 are independently selected from the group consisting of hydrogen, lower alkyl, and aryl.

25 19. A method of lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a pharmaceutical composition as recited in claims 1,2,3,4,5,6 and 7.

30 20. A compound having the formula:



thereof, wherein:

X is selected from the group consisting of methylene, nitrogen, oxygen, sulfur, SO, or SO₂;

5

n = 0 to about 7;

R¹ and R², are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thioalkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, alicyclic hydrocarbon, heterocycly, aromatic hydrocarbon, -CONR⁵R⁶, -SO₂nR⁵R⁶, -COR⁵, -SO₂R⁵, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate, and sulfonamide, wherein all said radicals are optionally substituted with one or more of the following:

hydroxy, alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carboalkoxy, carboaryloxy, carboxy alkylaryloxy, haloalkyl, -SO₂NR⁵R⁶ and -SO₂R⁵ wherein all said substitutions may be optionally substituted with one or more of the following:

amino, carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

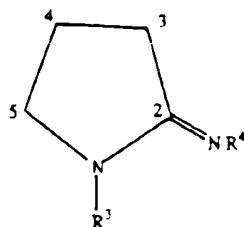
and R¹, R², may optionally together form an alicyclic hydrocarbon, heterocycly or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

35

R³, R⁴ are hydrogen, hydroxy, and alkyloxy;

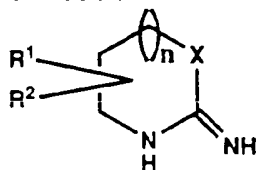
consisting of hydrogen, lower alkyl, and aryl;

with the proviso that when $n=1$



and R¹ and/or R² are at position 3 or 4, neither R¹ or R² is aryl and with the further proviso that when X is methylene, nitrogen, oxygen, or sulfur then R¹ and R² cannot be both H, or be a haloalkyl and where $N=3$ R¹ cannot be Methyl at position 7.

21. A pharmaceutical composition comprising a compound having the formula:



and salts, pharmaceutically acceptable ester and prodrugs thereof, wherein:

X is lower alkyl, nitrogen, oxygen, or sulfur wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;

n is an integer from 0 to about 6;

R¹ and R² are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, and haloalkyl wherein all said radicals may optionally be

haloalkyl groups and R^1 , R^2 may optionally form an alicyclic, heterocyclic or aromatic radicals; and together with at least one non-toxic pharmaceutical acceptable carrier.

22. The pharmaceutical composition defined in Claim 21 wherein:

- 5 X is lower alkyl of 1 to 3 carbon atoms, nitrogen, oxygen, or sulfur wherein nitrogen and lower alkyl radicals may optionally be substituted with hydroxy, lower alkyl, lower alkoxy, amino, and haloalkyl groups;
- 10 n is an integer from 0 to about 4;
- R¹ and R² are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl of 1 to about 6 carbon atoms, lower alkoxy of 1 to about 6 carbon
15 atoms, lower alkenyl of 1 to about 6 carbon atoms, lower alkynyl of 1 to about 6 carbon atoms, halogen, nitro, amino, carboxyl, cyano, sulfonyl, trifluoroalkyl and haloalkyl and wherein each said radical may optionally be substituted with hydroxy, lower alkyl of 1 to about 6
20 carbon atoms, lower alkoxy of 1 to 4 carbon atoms, lower alkenyl of 1 to about 6 carbon atoms, lower alkynyl of 1 to about 6 carbon atoms, halogen, nitro, amino, carboxyl, cyano, sulfonyl, and haloalkyl groups and R¹, R² may optionally form a 3 to 7-carbon membered alicyclic,
25 heterocyclic or aromatic radical.

23. The pharmaceutical compositions defined in Claim 21 wherein:

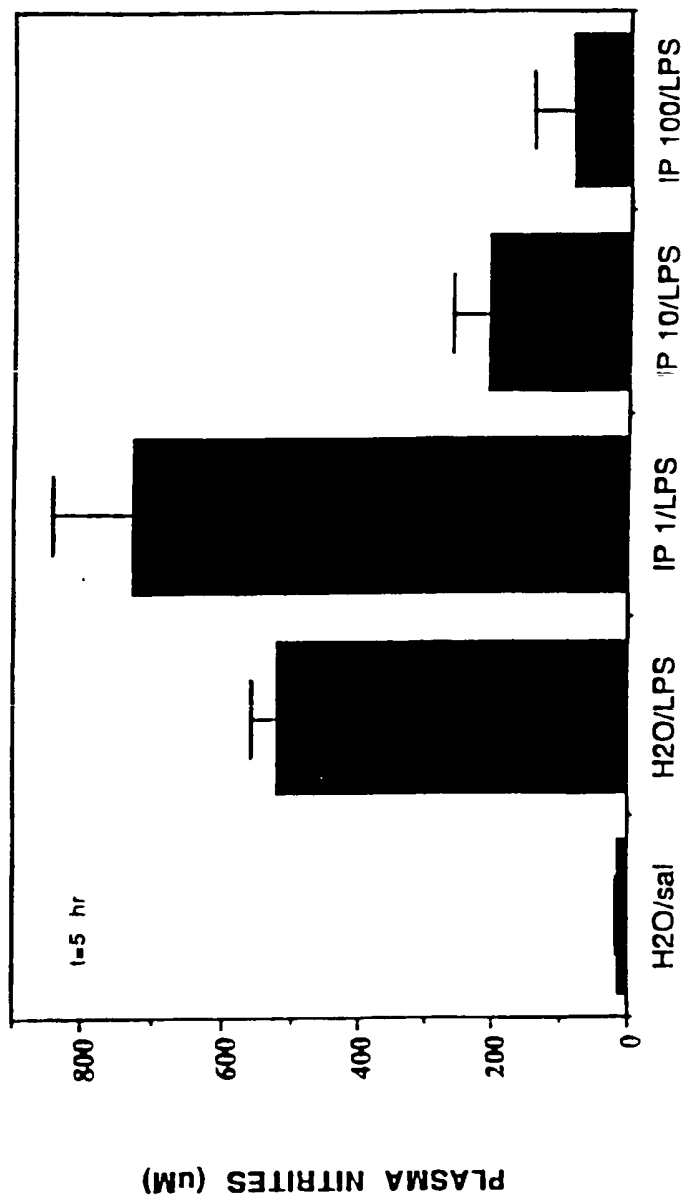
X is lower alkyl, nitrogen, oxygen, or sulfur wherein
5 nitrogen and lower alkyl radicals may optionally be substituted with lower alkyl, lower alkoxy and amino;

n is an integer from 0 to about 4;

10 R¹ and R² are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl of 1 to 3 carbon atoms, nitro, amino, carboxyl, and cyano and wherein all said radicals may optionally be substituted
15 with hydroxy, lower alkyl of 1 to 3 carbon atoms, lower alkoxy of 1 to 3 carbon atoms, halogen, nitro, amino, carboxy or cyano and R¹, R² may optionally form a 3 to 7-carbon membered alicyclic, heterocyclic or aromatic ring.

1/1

FIG. 1



INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 94/11832

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/22 C07D211/72 C07D215/38 C07D223/12 C07D225/02
C07D239/12 A61K31/40 A61K31/445 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 446 699 (MERRELL DOW) 18 September 1991 cited in the application see the whole document ---	1-23
P,X	WO,A,94 12165 (WELLCOME FOUNDATION) 9 May 1994 cited in the application see table 1, example 7 ---	1-23
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol.77, no.3, 10 February 1955, GASTON, PA US pages 761 - 762 'Cyclic Guanidines from Nitrimino Compounds' cited in the application see the whole document ---	20

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 February 1995

Date of mailing of the international search report

24.02.95

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 94/11832

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. CHEM. SOC., 1965 pages 474 - 479 '2-Amino-2-imidazolines and 2-Amino-2-oxazolines.' cited in the application see the whole document ---	20
X	J. CHEM. SOC., 1962 pages 4039 - 4045 'Hydropyrimidines' cited in the application see the whole document ---	20
X	JOURNAL OF ORGANIC CHEMISTRY., vol.33, no.5, May 1968, EASTON US pages 2109 - 2111 'Synthesis and Reactions of Cyclic Amidines' cited in the application see the whole document ---	20
X	JOURNAL OF ORGANIC CHEMISTRY., vol.39, no.13, 1974, EASTON US pages 1819 - 1823 '2-Amino-2-thiazoline' cited in the application see the whole document -----	20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 94/11832

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